Prehospital thrombolysis for acute ST-segment elevation myocardial infarction

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PREHOSPITAL THROMBOLYSIS
FOR ACUTE
ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

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CHAPTER 1

INTRODUCTION TO PREHOSPITAL THROMBOLYSIS

1.1 Introduction

Prehospital thrombolysis in Nijmegen

Every ten years prehospital thrombolysis is re-invented, said professor Mervyn Gotsman during a meeting of the European Society of Cardiology in Barcelona in 1999. Indeed, the earliest reports describing prehospital administration of thrombolytic therapy emerged from Jerusalem, from where Gotsman *et al* reported in the New England Journal of Medicine in 1985.[1] Following this, further studies were to appear in the international literature, not only concerning prehospital treatment, but the importance of early therapy in general, pioneered by the GISSI-report dealing with myocardial infarction and treatment with streptokinase.[2] Largely as a result of this, cardiologists in the Netherlands were made aware of the substantial delays involved in the treatment of acute myocardial infarction as normally carried out. Working in close cooperation with ambulance personnel, general practitioners and cardiologists, in 1987, Nijmegen s Canisius-Wilhelmina hospital then became the first to initiate a prehospital strategy in The Netherlands. Nijmegen was soon followed by Rotterdam, a similar program being started in 1988. From that time on, prehospital thrombolysis has had its roots in The Netherlands.

Nevertheless, prehospital thrombolysis was soon to be overshadowed by the impact of the in-hospital ISIS-2 trial, published in 1988, in which randomized treatments using aspirin and/or streptokinase, or neither, were administered to patients with suspected acute myocardial infarction.[3] To the surprise of all, these two relatively simple and inexpensive drugs could be applied to reduce in-hospital mortality by some 50%. This success soon pushed the relatively complicated, outside-hospital diagnosis of acute myocardial infarction, together with the concomitant prehospital drug supply required, along with the budget reallocations thus entailed, to the background. In the area of acute myocardial infarction, prehospital thrombolysis thus lost some of its momentum.

But not for long. Numerous studies on the effects of streptokinase and, later, rt-PA, appeared in the literature, leading to a renewed recognition of the various delays inherent in treating acute myocardial infarction.[4] Time delays were recorded[5] and hospital strategies were changed so as to reduce in-hospital treatment delays.[6] This renewed attention on the importance of speed restimulated interest in prehospital treatment, leading to the publication of three major

reports published in the early nineties,[7-10] involving randomized allocations of pre- versus in-hospital treatments. However, the long-expected reduction in mortality for the prehospital treated patient group failed to materialize. In fact, mortality reached statistical significance only in the GREAT study[8], in which prehospital therapy reduced the time to treatment by 130 minutes.
In retrospect, this randomization between prehospital and in-hospital treatments seems less of a good idea, allowing in both groups, as it does, patients presenting early as well as late after onset of symptoms. A better course is to analyse the outcome of patients with myocardial infarction according to their time to treatment. Boersma *et al* provided this analysis, publishing their reappraisal of the Golden Hour in 1996.[11] In this, early treated patients from previous studies of prehospital thrombolysis were included so as to provide data concerning treatment within the first hour after onset of symptoms.
That is, roughly 10 years following Gotsman s report on his experience with prehospital treatment in 1985, the real importance of treatment within one hour finally became clear. But only by means of prehospital therapy could treatment within the Golden Hour be achieved. And from that moment on, more or less, prehospital treatment became re-invented. Once the turning point of the Golden Hour had been reached, along came a new generation of easy-to-administer thrombolytics in single or bolus form ready for testing in the field. Furthermore, publications began to appear describing mechanical methods for the opening of blocked coronary arteries rather than thrombolytic therapy. But although the results of primary angioplasty in acute myocardial infarction were promising, the time to treatment reached with prehospital triage and thrombolysis could not be matched.

Basis for this thesis
In Nijmegen, prehospital therapy has been implemented since 1987. The aforementioned ups and downs in the history of prehospital treatment are reflected in the number of patients treated over the years. Following a learning process in the use of transtelephonic transmission for achieving prehospital diagnosis of acute myocardial infarction, only 10% or less of patients with acute myocardial infarction were actually treated prehospitally. Fax transmission of ambulance-ECG s from the CCU to the cardiologist s home during the early hours

(using the first generation fax machines of that time), was also initiated, in 1987. Following a period of training in the two Nijmegen hospitals involved in prehospital thrombolysis, in 1992 the author joined the advisory board of the Nijmegen ambulance service, together with two general practitioners from the region. Prehospital thrombolysis proved to be a good catalyst for improving cooperation among general practitioners, ambulance staff and hospital specialists. After a number of exploratory sessions involving cardiologists, general practitioners and ambulance crew, during which the principles of thrombolysis and importance of time to treatment were explained, the local advisory board of general practitioners made the decision to adopt prehospital diagnosis and thrombolytic therapy in their guidelines for standard family care. From that time on, inclusion of patients in the prehospital strategy increased again to about 75% of all patients with acute ST segment elevation myocardial infarction. The greater part of the Nijmegen patient database was built up at this time.

Hypotheses

According to the available literature (chapter 2) dealing with the importance of early treatment, no more than 25% of patients are treated within 2 hours using in-hospital thrombolysis. The number of patients treated within the golden hour is thus inevitably much smaller. Accordingly, our first question is: How many prehospitally treated patients can be treated within 1 or 2 hours after symptom onset, in comparison with those who receive in-hospital treatment? The STIMIS-study, discussed in chapter 3, is an attempt to answer this question. Whether the time gained using prehospital thrombolysis is specific to the Nijmegen situation or can be realized equally in other regions is discussed in chapter 4. In examining the data we can discern two groups of patients: those treated relatively early, and those treated relatively late. Can anything be said about the differences between these two in respect of prognosis? We hypothesize that early treatment results in fewer deaths and fewer heart failures than late treatment. Moreover, experience in practice has given rise to the concept of *aborted* myocardial infarction, a condition hitherto unrecognized in the literature. Mortality, heart failure and aborted myocardial infarction are examined in chapters 5, 6 and 7.

Primary angioplasty plays an important role in the treatment of acute myocardial infarction. Although associated with a very high reperfusion rate and low

mortality, there remain questions about the time to reperfusion and whether the concept of aborted myocardial infarction is applicable to primary angioplasty. Chapter 8 considers the results represented by a combination of databases from one of the Dutch leading primary angioplasty centres, Zwolle, together with our own prehospital database in Nijmegen.
New generation bolus thrombolytics are ideally suited to prehospital use. Chapter 9 discusses their effects on time to treatment, as revealed in a combination of our Nijmegen database with that of a second large prehospital thrombolysis centre in Rotterdam.
Ever since the introduction of thrombolysis, clinicians have been wary of unjustified fibrinolysis, a wariness that becomes only heightened in the prehospital situation. We compare two prehospital databases, the data in each based upon differing ECG methods for the diagnosis of acute myocardial infarction, in an attempt to explain their relative incidence of unjustified fibrinolysis. Finally, it is clear that the introduction of prehospital thrombolysis must entail hospital budget re-allocations, and this in a health system notoriously preoccupied with costs. In chapter 11, different methods are applied for the calculation of the cost per life year gained with prehospital thrombolysis as compared with in-hospital treatment.
In summary, the following questions are to be answered:

1. Looking at different regions across The Netherlands, what is the time to treatment, and what percentage of patients is treated within one and two hours, respectively, by means of prehospital therapy?
2. How do mortality, incidence of heart failure, and incidence of aborted myocardial infarction compare in the early and late treatment groups using prehos-pital versus in-hospital thrombolysis?
3. Is the incidence of aborted myocardial infarction the same in primary angioplasty as it is in prehospital thrombolysis?
4. Is there a difference in time to treatment using newer generation bolus therapy, as opposed to the current infusion strategy, when we compare two regions in which prehospital thrombolysis is an established therapy?
5. What is the incidence of unjustified fibrinolysis using two different means of ECG-diagnosis?

6. What is the cost per life year gained by prehospital thrombolysis in our region?

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Chapter 2

The importance of early treatment of ST-segment elevation myocardial infarction; a review

2.1 Definition of acute myocardial infarction

Cell death

Central to the definition of acute myocardial infarction is the loss of cardiac myocytes, caused by prolonged ischaemia. Ischaemia is caused by the imbalance of demand and supply of oxygen. In most cases this imbalance is initiated by rupture of an atherosclerotic plaque, followed by thrombosis, which gives rise to total occlusion of a coronary artery.[1]

The loss of cardiac myocytes is measured by the release of various markers in blood samples. Electrocardiographically, the loss of cardiac myocytes is accompanied by ST-segment changes and/or the development of pathological Q-waves. Using imaging techniques such as echocardiography or radionuclide techniques, the loss of myocardial tissue can be detected by wall motion abnormalities and/or the loss of tissue perfusion. One must realize that the defining characteristic of myocardial infarction, cell death, is a histopathologic event and that the development of cell death costs time. After coronary occlusion, at least 15 minutes must pass before an ischemic myocyte dies. It takes at least 6 hours before myocardial necrosis can be identified with standard pathology techniques, and this time span depends on the presence of collateral blood flow and the sensivity of myocytes for ischemia. So, time plays a considerable role in the development of cardiac necrosis, and thus in the efforts to limit the impact of ischaemia.

Classification of myocardial infarction in time

Myocardial infarcts are classified according to their histopathologic appearance as *acute* (6—12 hours from onset of symptoms), *ongoing* (from 12 hours to 7 days), *healing* (7 days to 28 days) and *healed* (from 28 days onward). No or only minimal histopathologic characteristics of cell death may be found in myocardial infarctions with symptoms less than 6 hours.

WHO definition of acute myocardial infarction

In the past the World Health Organisation defined acute myocardial infarction as the combination of two of three characteristics: (1) typical symptoms of myocardial infarction (chest pain or discomfort), (2) typical enzyme rise (creatinephosphokinase and cardiac aspartate aminotransferase) and (3) a typical

ECG pattern with ST-segment elevation and development of Q waves. It is important to note that in this definition typical enzyme rise is not necessary, as only two characteristics are needed. However, in the wake of the development of more specific serologic markers and image techniques, problems arose in defining myocardial infarction as we used to know it. The specific markers such as the troponins identify patients with small infarctions that would not be considered to be an infarction according to the WHO definition. So new definitions of acute myocardial infarction were proposed.[2]

Most recent definition of acute myocardial infarction
In the newest definition of myocardial infarction, recorded cell death fulfills a more central role than in the WHO-definition. Cell death must be made plausible by a typical course of biochemical markers, such as troponin-I or —T, CK or CK-MB, or signs of myocardial necrosis by histopathologic investigation. These must be accompanied by at least one of the following signs:

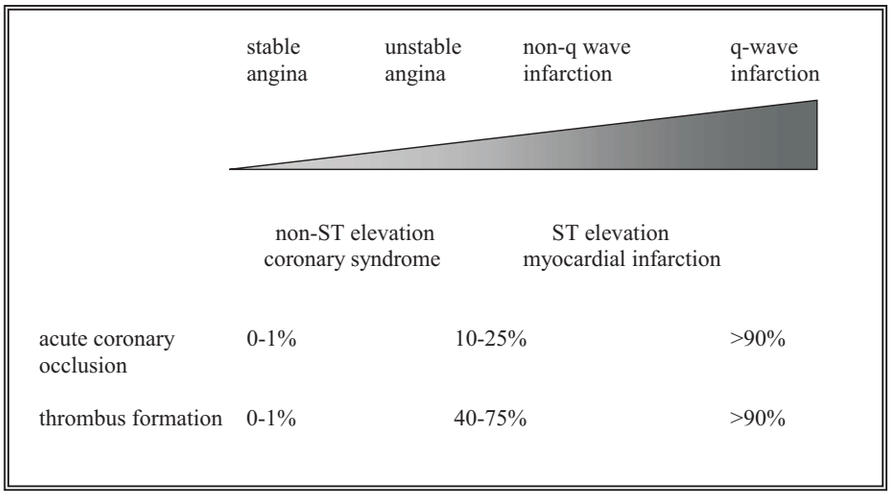
- typical symptoms
- development of Q waves on the ECG
- ECG-signs of ischaemia (ST-segment elevation or depression)
- The above in the wake of coronary intervention such as angioplasty

Troponin-I or -T have almost absolute myocardial tissue specificity, as well as a high sensivity, so measuring this marker can be regarded as the golden standard for assessing myocardial damage. CK-MB is the best alternative for troponins, although less tissue-specific. As with cardiac troponin, an increased value is defined as one that exceeds the 99th percentile of CK-MB values in a reference control group. Total CK is less specific, and the cut-off limit is regarded as at least twice the upper reference limit for CK. The degree of increase is related to the extent of the damage, but must be seen together with other clinical factors, such as signs of reperfusion, development of definitive Q-waves and loss of voltage on the ECG and signs of residual left ventricular function.

ST elevation myocardial infarction versus other categories
With these new serum markers of myocardial cell death new categories of

acute myocardial infarction present themselves, each with their own histopathologic characteristics (fig 2.1-1). In these definitions all patients with non-ST elevation and ST elevation myocardial infarction and some with unstable angina pectoris will have a rise in troponin-I or T. These are all caused by acute changes in a coronary atherosclerotic plaque and all have their own prognosis, treated or not.

Figure 2.1-1. Acute coronary syndrome and its histopathologic characteristics. Adapted from [3].



Acute coronary syndromes in this thesis

In the following text we concentrate on the acute coronary syndrome characterized by ST-segment elevation on the presenting ECG. Although signs of cell death are pivotal in the latest definition of acute ST elevation myocardial infarction, one must realise that patients can be treated in such a way and within such time span that cell necrosis is averted. These patients present themselves with pain and ST-segment elevation on the ECG but, usually after some sort of intervention, there is no significant rise in cardiac enzymes. In such patients myocardial infarction is *aborted*.[2] Although this possibility is mentioned in the various reviews about acute coronary syndromes[2,3], it is not elaborated further in these texts.

Thrombolysis and ST elevation myocardial infarction

To start therapy with thrombolysis acute ST elevation myocardial infarction

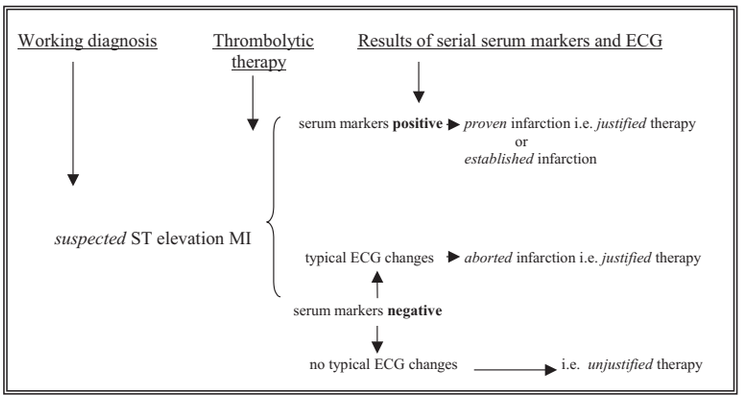
must be suspected, but of course can not be proven, because the latter is only possible by a rise in cardiac enzymes, which is time dependent. The combination of chest discomfort together with ST-segment elevation points to *suspected* acute myocardial infarction, whereas these two criteria plus a rise in cardiac enzymes diagnoses *proofs* acute myocardial infarction. In the case of suspected acute myocardial infarction, not followed by a rise in cardiac enzymes, there are two possibilities:

- Acute myocardial infarction and its cell death is averted, i.e. aborted myocardial infarction.
- There has been no acute myocardial infarction, but another cardiac or non-cardiac condition causing chest pain together with ST-segment abnormalities on the ECG, but not accompanied by myocardial necrosis.

In trials of acute ST elevation myocardial infarction there has been different thresholds for the rise of cardiac enzymes. Usually a threshold of CK-MB of twice or more the upper limit of normal has been taken to identify myocardial damage.[2]

ST elevation myocardial infarction in this thesis
So, in the following text acute ST elevation myocardial infarction is defined as (fig 2.1-2)

Fig 2.1-2. Acute ST elevation myocardial infarction and thrombolytic therapy in this thesis.



MI = myocardial infarction

- *suspected*, based on chest comfort and ST-segment elevation on the ECG characteristic of acute myocardial infarction

On this ground treatment can be started; following results of serial ECG s and blood samples:

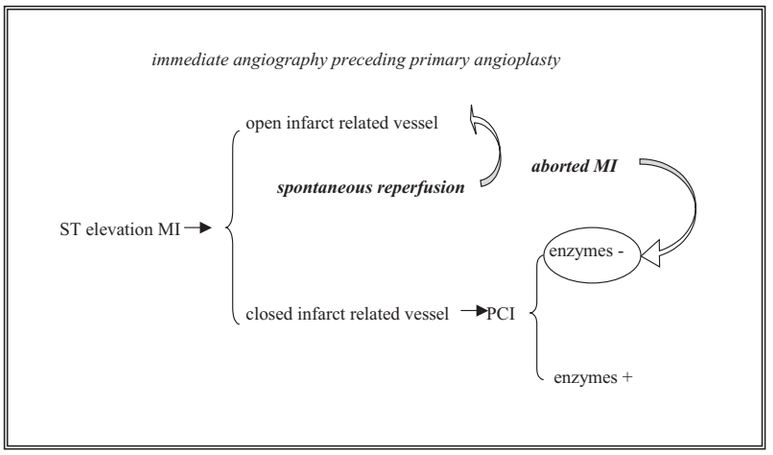
- the infarction has been *proven*, or *established*, based on the above criteria, with a rise in cardiac enzymes more than twice the upper limit of normal
- the infarction has been *aborted,* or *reversed,* which is a suspected acute myocardial infarction with dynamic ECG changes, but not accompanied by a rise in cardiac enzymes more than twice the upper limit of normal.

Treatment based on the suspicion of myocardial infarction, ending in either aborted or proven myocardial infarction was *justified*. If the diagnosis after serial ECG s and blood samples proves to be incorrect, the treatment was *unjustified*. The role of the rise of cardiac enzymes is important, because an aborted myocardial infarction, based on a not significant rise of cardiac enzymes, can be viewed as the ultimate goal of therapy; unjustified treatment, with its danger of inducing side effects and complications of the drug, clearly is not.

Spontaneous reperfusion

Aborted myocardial infarction may be confused with *spontaneous reperfusion*. DeWood found in 16 of 126 patients (13%) an open infarct related vessel,[1] using angiography which was performed within 4 hours after onset of symptoms. All these patients had symptoms and ECG-changes consistent with acute myocardial infarction, *together with a rise in cardiac enzymes*. Spontaneous reperfusion is confirmed by the results of primary angioplasty for acute ST elevation myocardial infarction, and the primary angioplasty studies can be used to demonstrate the difference between spontaneous reperfusion and a borted myocardial infarction (fig 2.1-3). The incidence of TIMI 2-3 flow for patients with ST elevation myocardial infarction presented for primary angioplasty varies between 13 and 19.6%, [4-6] comparable with the results of De Wood. The difference between spontaneous reperfusion and abortion of myocardial infarction is the rise in enzymes in the first condition, and its absence in the latter.

Fig 2.1-3. Difference between aborted myocardial infarction and spontaneous reperfusion, as demonstrated with primary angioplasty



MI = myocardial infarction
PCI = percutaneous coronary intervention (angioplasty)

In summary, the newest definition of acute ST elevation myocardial infarction consists of characteristic symptoms plus ECG-changes plus evidence of cell death measured by troponins, or, less specific, CK-MB and transaminases in the patients blood samples. To start an intervention as thrombolysis or primary angioplasty, the rise in serum markers is not needed, and treatment can be administered according to a suspicion of the diagnosis. This can result in *justified* therapy, ending in *proven* or *aborted* infarction, or *unjustified* therapy, if the suspicion of acute ST elevation myocardial infarction was incorrect.

2.2 The wave front phenomenon of myocardial necrosis of acute myocardial infarction: time to reperfusion, myocardial damage and viability

When time to treatment after onset of pain in acute myocardial infarction is concerned, often is referred to experiments done by Reimer & Jennings[7] and Bergmann,[8] who investigated the extent of myocardial damage as a function of time. These authors preceded the routine use of thrombolytic agents for acute myocardial infarction by about 5 years; much of the benefits of early treatment were based on the results of these experiments. Because of the emphasis laid

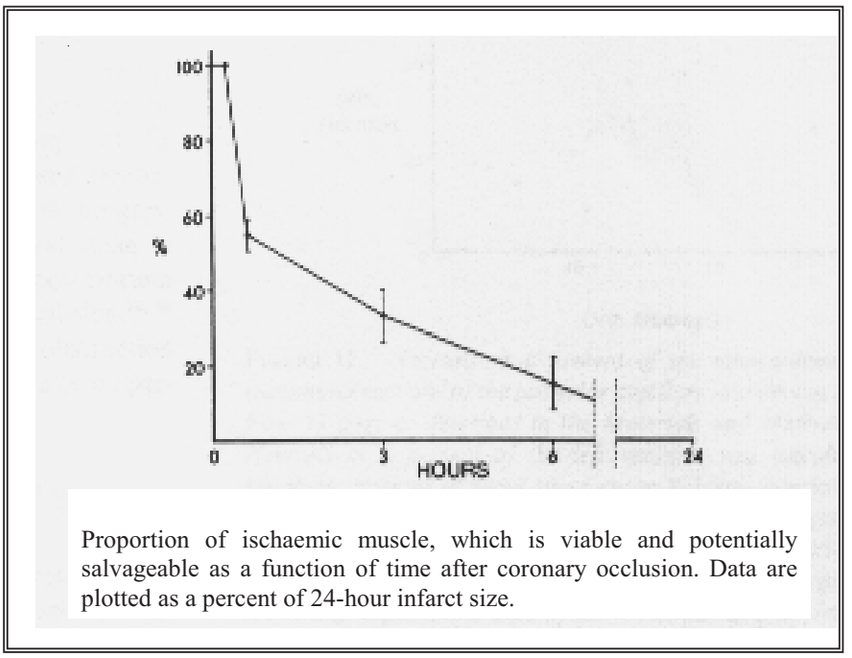
on the time to treatment in the following chapters, it seems apt to summarize these classical experiments and discuss their results.

Salvage of myocardial tissue as a function of time
Reimer & Jennings hypothesised that myocardial tissue could be salvaged if the occlusion of the coronary artery was limited in time. The duration of the period dictating the amount of necrosis being unknown, the authors set up experiments, in which instrumentated dogs were exposed to coronary occlusion of various duration, after which the amount of viable and necrotic myocardial tissue was determined.
Mongrel dogs (n=58) were operated upon in such a way that the circumflex coronary artery could be occluded and reopened. The dogs were assigned to five groups: one group had a 40 minute occlusion, one group a 3 hour occlusion and one group a 6 hour occlusion. In 2 other groups the occlusion was permanent and these dogs were sacrificed at 24 and 96 hours respectively, together with the dogs from the other 3 groups with reperfusion. The extent of necrosis was determined by various means of quantitative stain techniques, whereby the amount of necrosis was expressed as the overall percentage of a transmural slice cut from each heart.

All dogs showed myocardial necrosis. The dogs exposed to 40 minutes occlusion showed necrosis throughout the region supplied by the circumflex artery, but the necrosis was restricted to the subendocardial myocardium. The hearts reperfused after 3 and 6 hours of coronary occlusion showed considerable larger areas of necrosis, extending from the subendocardial layer to the subepicardial myocardium, the latter especially in the group with six-hour occlusion. It is important to note that 55% of the affected ischemic myocardium remained viable when reperfusion was implemented after 40 minutes. Less than 17% remained viable when reperfused after 6 hours (fig 2.2-1). In the 3- and 6-hour occlusion groups subendocardial haemorrhage was also prominent. These areas of haemorrhage surrounded areas of myocardial tissue undergoing autolysis; in the subepicardial myocardium, however, the areas with autolytic material were interspaced with islands of viable cells, often adjacent to small penetrating arteries, with signs of inflammation and repair. Infarcts resulting from permanent coronary occlusion were very similar to those resulting from 6 hours of

temporary occlusion, differing most according to the age at sacrifice. At 24 hours haemorrhage was relatively mild, at 96 hours of permanent occlusion haemorrhage was prominent and appeared equivalent to haemorrhage produced in 3 and 6 hours of temporary occlusion.
The authors concluded that in dogs with both temporary and permanent occlusion of the circumflex artery a wavefront of irreversible ischaemic injury occurs, first of all endocardially and gradually extending towards the subepicardial layers of myocardium. The development of this wavefront takes about 6 hours. Reperfusion later than 40 minutes cannot prevent subendocardial necrosis,

Fig 2.2-1. Proportion of ischaemic muscle, viable as a function of time to reperfusion. From[7] with permission.



Proportion of ischaemic muscle, which is viable and potentially salvageable as a function of time after coronary occlusion. Data are plotted as a percent of 24-hour infarct size.

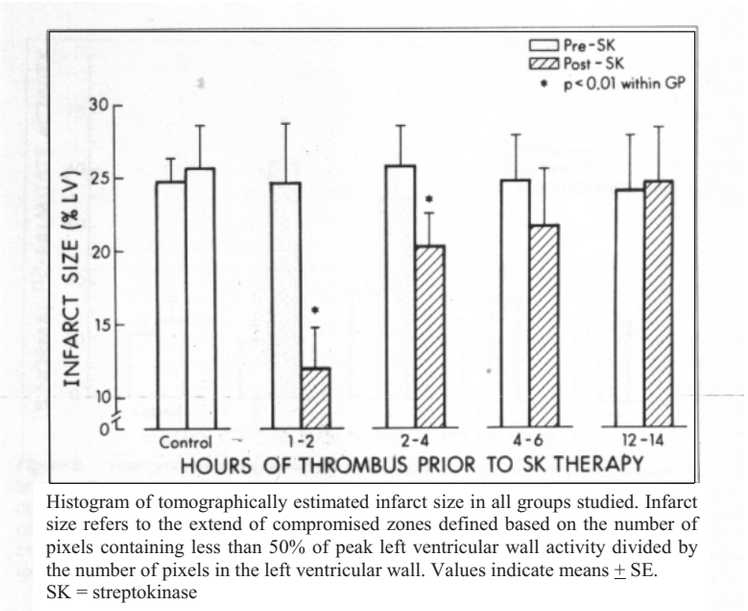
which after 6 to 24 hours is almost transmural. The authors explained this wavefront from subendocardial to subepicardium by the distribution of the coronary collateral blood flow. Reperfusion preserved viable myocytes, accelerated the disruption of irreversible damaged myocytes and induced inflammation and repair. Furthermore, reperfusion is associated with interstitial

haemorrhage from vessels which had been injured but not occluded at the time of reflow, but had no effect on areas which became nonperfusable. Viability of ischemic myocardium is a function of time before reperfusion and is lost after about 6 to 8 hours. Interstitial haemorrhage is undesirable, because it is followed by the occurrence of no reflow, which results in further deterioration of the myocardial function.

Positron emission tomography and salvage of myocardium

Bergmann *et al* refined these experiments by using positron emission tomograms to assess the salvage of myocardium jeopardized by ischaemia.[8] Positron emission tomography measures the metabolic integrity of myocardium, and is useful to assess whether an intervention has lead to maintenance or restoration of myocardial viability. Intracoronary streptokinase was used to reperfuse experimentally induced thrombotic artery occlusion, also in dogs. Twenty-three dogs were instrumentalized and thrombotic coronary occlusion was induced. Reperfusion was created by intracoronary administered streptokinase at different time intervals: 1-2 hours after reperfusion (4 dogs), 2-4 hours (6 dogs), 4-6 hours (4 dogs) and 12-14 hours (3 dogs). The response to reperfusion varied with the duration of the occlusion. Six dogs did not undergo reperfusion and served as controls. Positron emission tomography was performed before streptokinase was given and repeated after establishing reperfusion by angiography. No change of expected infarct size occurred in dogs without thrombolysis (fig 2.2-2). Occlusion for one to two hours led to an about 50% decrease of metabolic compromised zones and to a 50% decrease of expected infarct size. In contrast, reperfusion after 6 hours resulted in no significant salvage. The authors could not establish rescue of myocardium after occlusion for more than 90 minutes in these experiments with dogs, even after angiograpically demonstrable lysis of thrombus.

Fig 2.2-2. Estimated and real infarct size as calculated from positron emission tomography before and after streptokinase. From [8] with permission.



Histogram of tomographically estimated infarct size in all groups studied. Infarct size refers to the extend of compromised zones defined based on the number of pixels containing less than 50% of peak left ventricular wall activity divided by the number of pixels in the left ventricular wall. Values indicate means ± SE. SK = streptokinase

Although half of the ischemic myocardium that was necrotic at 24 hours has already died at 40 minutes, about a third of this area was still salvageable at 1 to 4 hours, whereby most of the myocardial tissue at risk could be salvaged if reperfusion is established within 1 hour.

Salvage of myocardial tissue and stunning of myocardial infarction

In a recent article[9] these classic experiments have been reviewed together with more extensive explanation of the harmful effects of reperfusion. Within 8 seconds of a sudden occlusion of a major branch of a coronary artery of a dog a shift from aerobic to anaerobic glycolysis appears, followed by stretching rather than shortening of myocardial tissue. Intracellular high energy phosphates decrease after 30 seconds of ischemia, whereby anaerobic glycolysis is not able to provide enough high energy phosphate and the amount provided is produced very inefficiently with accumulation of lactate, decreasing the intracellular pH after 10 minutes of ischaemia. Sudden restoration of arterial flow to ischemic myocardial tissue produces marked hyperemia, with its peak dur-

ing the first 5 minutes of reperfusion. Arterial flow returns to control after about 20 minutes of reperfusion. Together with a rise of O_2-derived free radicals, marked mitochondrial and cell swelling appear. After about 2 minutes the intracellular pH has been returned to normal levels. It will take many hours to resynthesise the depleted pool of high-energy phosphates. An unexpected by-product of reperfused, reversibly injured myocardium is, that it is preconditioned to overcome another ischemic period, in such a way that it will tolerate another episode, which can be longer than the first episode of ischemia. Although the myocardium is reperfused and cell death is prevented, the myocardial tissue exhibits temporary contractile failure, which has been called stunning . This phenomenon lasts hours to days before function is totally restored. An important property of stunned myocardium is, that it is able to contract when exposed to inotropic agents like dobutamine or dopamine. Some experiments show that stunning is the effect of the oxygen-derived free radicals, generated during reperfusion; however, stunning is also dependent on the time the myocardial tissue has been ischemic.
This research has been performed to try to limit the infarct size by pharmacological or other interventions. Although convincing in the instrumentated dog, these experiments could not automatically be translated to humans with acute ST elevation myocardial infarction. In man, the impact of coronary occlusion is dependent on the underlying atherosclerotic disease in the coronary arteries, the extent of the collateral network and the patency of the coronary artery after 24 hours, when viability of the myocardium at risk is supposed to be lost.[9] To assess the importance of early treatment in humans, thrombolytic trials have been analysed in the literature, and outcome related to the time of treatment.

2.3 First reports of the importance of early treatment in man

After recognition of streptokinase as an agent to lyse human blood clots in 1933, it was used for acute myocardial infarction in 1954, with the first series of patients reported in 1958.[10,11] Several studies followed, but acceptance of streptokinase was limited, probably because of the unclear pathophysiology of acute myocardial infarction at that time.[3] One of the largest of those early trials was reported by the European Cooperative Study Group and involved 512

patients treated with placebo or intravenous streptokinase and reported halving the 6-month mortality in the treatment group.[12] Although the benefit of intravenous administration was thus established, attention was drawn to intracoronary use of the drug. Treating patients with acute ST elevation myocardial infarction using intracoronary streptokinase was associated not only with a better survival,[13] but also with limitation of infarct size as showed by a better left ventricular performance in patients randomised to streptokinase compared to those randomised to control treatment.[14,15] Intracoronary administration limited the possibility of treating patients with acute myocardial infarction to hospitals with angiography facilities. This meant the transport of patients to these centres, with considerable consequences in time to treatment; furthermore, intracoronary administration was not without risk.[16] Therefore, efforts were made to introduce an easier and faster way of therapy. Intravenous thrombolysis with streptokinase appeared again, first in combination with intracoronary streptokinase,[17] later on its own, resulting in a comparable reperfusion rate and mortality reduction when administered in either way.[18,19]

The GISSI-1 study

From 1986 onwards, reports were published on trials proving the efficacy of intravenous thrombolysis. The GISSI study, published in 1986[20] and 1987[21], was the first to show that the reduction of mortality in patients treated with intravenous thrombolytic therapy was related to the time of treatment. In 176 Cardiac Care Units in Italy 11,712 patients with chest pain and ECG-abnormalities suggesting acute myocardial infarction were evaluated. They had been randomised between streptokinase and control. The 21-day mortality rate as the 12-month mortality rates showed significant reduction (table 2.3-1).

Table 2.3-1. Results from the GISSI-reports. From[20,21].

	All patients n=11,712	**Streptokinase N=5,860**	**Placebo n=5,852**	**p (log-rank)**	**RR**
21-day mortality	11.8%	10.7%	13.0%	0.0002	0.81
	All patients n=11,697	**Streptokinase N=5,851**	**Placebo n=5,846**	**p (log-rank)**	**RR**
12-month mortality	18.1%	17.2%	19.0%	0.008	0.90

RR = relative risk.

Furthermore, an even larger mortality reduction of 21% was found in patients treated with streptokinase within 3 hours, compared to patients treated later than that (table 2.3-2).

Table 2.3-2. Mortality difference according to time of treatment. GISSI-1 study.[21]

12-month mortality	**Streptokinase**	**Control**	**All patients**
TTT≤ 3 hours from onset	15.1% 456/3012	17.3% 532/3073	16.2% 988/6085
TTT> 3 hours from onset	19.4% 548/2829	20.9% 578/2760	20.1% 1126/5589

TTT = time to treatment

Mortality reduction of patients treated with streptokinase later than 6 hours was not significantly greater than of patients in the control group. Consequently, patients treated with streptokinase within 1 hour showed the greatest benefit, compared with patients treated with placebo (table 2.3-3).

Table 2.3-3. 12-month mortality and time to treatment. GISSI-study.[21]

Mortality	Total %	Streptokinase %	Control %	RR %	p
TTT≤ 1 hour	17.1	12.9	21.2	0.61	0.00001
TTT≤ 3 hours	16.2	15.1	17.3	0.89	0.02
TTT 3-6 hours	19.7	18.3	21.2	0.87	0.02
TTT 6-9 hours	21.2	21.1	21.4	0.98	n.s.
TTT 9-12 hours	20.1	21.9	18.5	1.18	n.s.

TTT = time to treatment, RR= relative risk, n.s. = not statistically significant

Although mortality reduction was greatest in the patients treated early, it was immediately clear that not many patients could be treated within 1 hour: only 1275 patients of the 11697 (11%) received their treatment (streptokinase or not) within this time frame.

ISIS-2 and GUSTO-I

From the many trials favoring thrombolytic therapy, the ISIS-2 trial, published in 1988,[22] and the GUSTO-I trial, published in 1996,[23] also highlighted the importance of early treatment.

The ISIS-2[22] study tested the risks and benefits of streptokinase alone, aspirin alone, and the combination of aspirin and streptokinase, against placebo in patients suspected of acute myocardial infarction. A total of 17,187 patients were enrolled. Mortality reduction versus placebo was greatest for the combination aspirin plus streptokinase group (35-day mortality reduction of 42%),

especially in those patients treated within 6 hours after onset of pain (35-day mortality reduction of 53%). These findings concurred with those of the AIMS study, reported in the same year. In this study, patients were treated with anistreplase or placebo, and it showed an extra 35% 30-day mortality reduction in the 334 patients treated within 4 hours with anistreplase compared with 168 patients treated later than that.[23]

In the GUSTO-1 trial[24] 41,021 patients with ST-segment elevation acute myocardial infarction were randomised to one of 4 thrombolytic treatments: rt-PA followed by intravenous heparin, intravenous streptokinase followed by intravenous heparin, intravenous streptokinase followed by subcutaneous heparin or half dose intravenous recombinant tissue-Plasminogen Activator (rt-PA) plus streptokinase. The results were classified according the time of treatment, with 10,611 patients treated within 2 hours, 20,213 patients treated between 2 and 4 hours, 7,650 patients treated between 4 and 6 hours and 1,359 patients treated later than 6 hours. Only 26.6% of patients were treated within 2 hours of symptom onset. Increasing with the time to treatment were overall mortality, stroke, shock and congestive heart failure, with less or no obvious increasing percentages of re-infarction and ischemia (table 2.3-4).

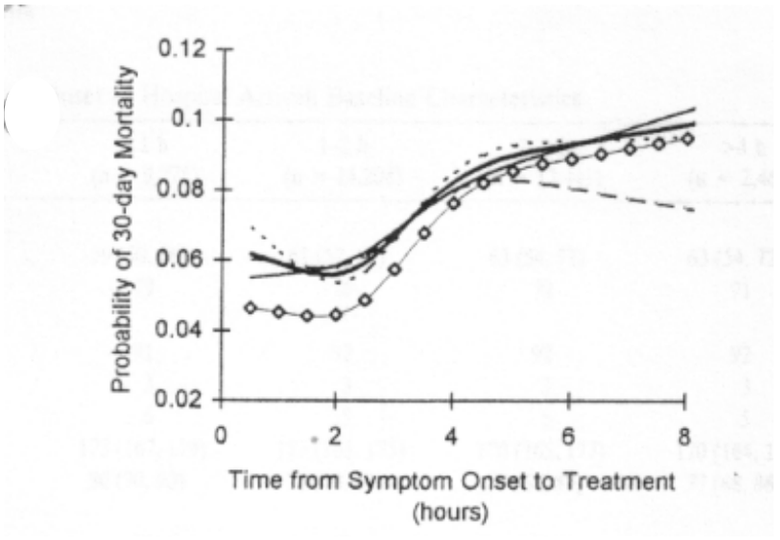
Table 2.3-4. Time from symptom onset to treatment related to clinical events; GUSTO-1 study.[24]

	TTT ≤ 2 hours n=10,611	**TTT 2-4 hours n=20,213**	**TTT 4-6 hours n=7,650**	**TTT > 6 hours n=1,359**
In-hospital mortality	5.3%	5.9%	8.5%	8.9%
Stroke	1.3%	1.5%	1.6%	2.0%
Re-infarction	4.7%	4.0%	3.2%	3.6%
Recurrent ischaemia	21%	20%	19%	18%
Shock	5.7%	5.6%	6.4%	7.0%
Congestive heart failure	14%	16%	19%	19%

TTT= time to treatment

Although there was a greater benefit in patients treated earlier, no significance could be found for the one thrombolytic therapy rather than the other (fig 2.3-1), with the exception of anterior infarction, which showed better mortality when treated with rt-PA.

Fig 2.3-1. Mortality related to treatment from onset of symptoms. From [24] with permission.

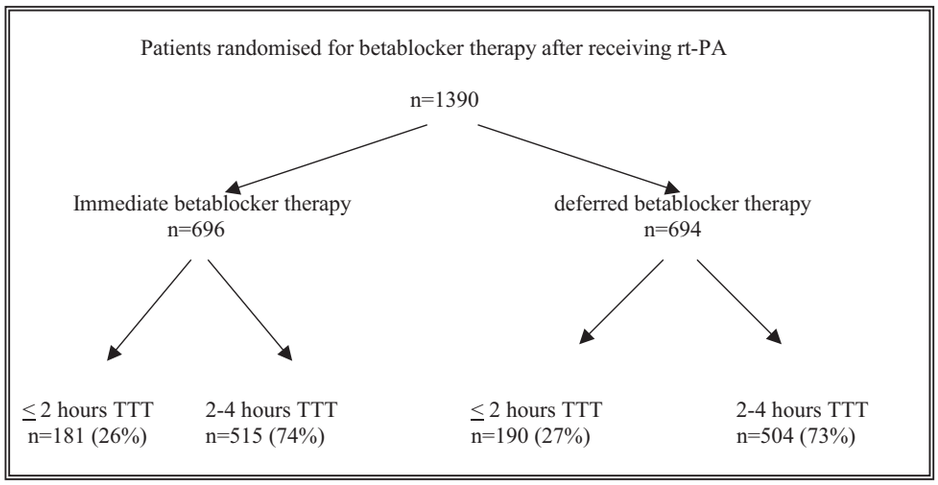


Probability of 30-day mortality as a function of time from symptom onset to treatment and assignment to streptokinase with subcutaneous heparin (short dash), streptokinase with intravenous heparin (light solid line), streptokinase and tissue-type plasminogen activator (t-PA) with intravenous heparin (long dash) or accelerated t-PA with intravenous heparin (line with diamonds). The heavy solid line shows the probability for the combined streptokinase groups.

The TIMI-2 study

The TIMI-2 trial[25] was designed to study the effect of immediate angioplasty compared to conservative treatment after rt-PA for patients with acute myocardial infarction. Of the 3,262 patients enrolled in this study a subgroup of 1,390 patients was randomised to be treated with early or with deferred betablockade (fig 2.3-2).

Fig 2.3-2. Patients of TIMI-2 substudy treated within or later than 2 hours.[25]



TTT=time to treatment with rt-PA

Analysis of these patients showed a significant lower 6-week mortality or recurrent myocardial infarction in the patients treated within 2 hours after onset of symptoms, compared to patients treated later (table 2.3-5). The 6-week mortality was especially better in the patients treated within 1 hour (3.2%) than in patients treated later. There was also a benefit of early treatment on left ventricular function. Incidentally, only immediate beta-blocker therapy had a significant effect in diminishing recurrent ischaemia. The TIMI-2 group observed that for each hour earlier that patients were treated with thrombolytic therapy the absolute mortality was reduced by 1%.

Table 2.3-5. Time from symptom onset to treatment with rt-PA and mortality. TIMI-2 substudy.[25]

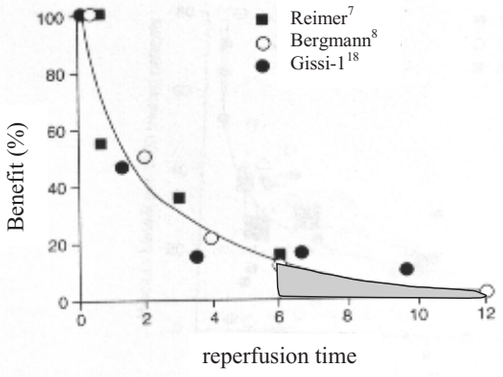
	Immediate betablocker n=696		**Deferred betablocker n=694**	
Time to treatment	< 2 hours n=181	2-4 hours n=515	< 2 hours n=190	2-4 hours n=504
Mortality and recurrent MI at 42 days	9 (5.0%)*	42 (8.2%)*	23 (12.1%)**	43 (8.5%)**

MI = acute ST elevation myocardial infarction.
* p=0.01, **p=0.83

Benefit of early time to treatment

Using combined data from the Reimer & Jennings and Bergmann experiments and from the GISSI-1 study, which represented the time-dependent benefit of coronary reperfusion, Tiefenbrunn[26] drew a time-benefit curve, extrapolating to early treatment (fig 2.3-3). From this curve we learn that the highest reduction in mortality is achieved in treatment within one or two hours, although the author referring to this data admits that only 5% or less of patients are indeed treated within this time frame. As can be seen from figure 2.3-3, after 6 to 12 hours there is still a small benefit to be gained from thrombolysis.

Fig. 2.3-3. Time benefit from reperfusion. From [26] with permission



Reperfusion time-benefit curve depicts combined data representing the time-dependent benefit anticipated depending on the interval between coronary artery occlusion and reperfusion; data from Reimer et al[7], Bergmann et al[8], and GISSI-1.[18] The shaded area represents an estimate of the portion of total benefit that is not time-dependent. Benefit (%) indicates percentage of myocardial salvage and percentage reduction in mortality.

Benefit of early treatment with other than thrombolytic drugs

The early administration of other than thrombolytic drugs may benefit the outcome of patients with ST elevation myocardial infarction. Of 1,720 patients in a recently published study using primary angioplasty for acute ST elevation myocardial infarction,[27] a group of 860 patients were prehospitally treated with heparin and aspirin. The other group was treated after arrival at the hospital. Both groups had a successful angioplasty in 92% and 90% of patients respectively. Prior to angioplasty there was a significant higher incidence of TIMI 3 flow in the prehospitally treated patient group, compared with the hospital treatment group (17% versus 10%). Pre-treatment with aspirin *before* thrombolytic administration results in a lower mortality (both 7 days as 1 year) than giving aspirin *after* thrombolytic therapy. This according to a study with 364 patients treated before and 836 patients treated after thrombolysis.[28] Both studies suggest a time dependent benefit from aspirin and heparin or aspirin alone for ST elevation myocardial infarction.

2.4 Prehospital and in hospital thrombolysis; trials and meta-analysis

Shortly after the importance of time to fibrinolysis became clear, attempts have been undertaken to shorten the various time delays in the treatment of patients with acute myocardial infarction.
The delays can be divided into 5 phases: patient delay, doctor s delay, on-scene time and transport delay, door to needle delay and the time it takes for the thrombolytic drug to establish reperfusion.[29] The first delay can hardly be influenced[30] and the last delay is characteristic of the specific drug to be used. Patient s delay is the time from symptom onset to seeking help, presentation delay the combination of patient s delay, doctor s delay, on-scene time and transport delay. In the 41.021 patients of the GUSTO-I study, patients characteristics were related to time to treatment variables.[24] The study investigated 3 variables: time from symptom onset to hospital arrival (presentation delay), time from arrival to initiation of therapy (treatment delay) and total time to treatment. Overall time to treatment < 4 hours was found in 77% of patients, with only 27% of patients treated within 2 hours. Female, hypertensive and diabetic patients were found in greater proportions in the later treatment groups, as were patients with prior myocardial infarction. On the contrary, current or former cigarette smokers were more frequent in the earlier group. Another study confirmed the presentation delay of female patients from a registry of 1178 patients.[31] The presentation delay of a mean of 1.89 hours was 49 minutes longer for women than for men. Not only the patient s delay, but also the in hospital delay was longer in female patients. Probably less typical symptoms can explain these time differences, but also other factors, like time of day, symptom severity and whether advice is sought from co-workers or family members.
In this section attention is drawn to the attempts to shorten the delay caused by transport to the hospital and the in-hospital delay, by administering thrombolysis prehospitally. From 1989 onwards, reports have been published about the feasibility of diagnosing acute myocardial infarction prehospitally, with the introduction of the administration of fibrinolysis before the patient is transported to the hospital. Later on, reports of studies were published in which patients were randomised between prehospital and in-hospital treatment, in order to try to establish the mortality reduction expected on the basis of early treatment.

Gotsman[32] was the first to show that diagnosis and treatment of myocardial infarction prehospitally was safe and feasible. Since then many reports about early and prehospital thrombolysis have been published.[33] Time measurements from 8 cities in the United States showed a remarkable uniform delay from hospital admission to initiation of thrombolytic therapy (average 83.8 minutes),[34] which emphasized the importance of prehospital treatment even further. Three basic protocols for prehospital thrombolysis exists: (a) physician operated mobile intensive care unit, (b) prehospital physician evaluation followed by mobile intensive care unit and (c) paramedic evaluation with ECG-transmission of one way or another. In a review of these protocols a potential time saving was observed of about 60 minutes with the protocol using paramedic evaluation and ECG-transmission, and this was expected to become the accepted method for diagnosing and treating acute myocardial infarction.[33] Since then a number of randomised trials have been done to compare pre- and in-hospital thrombolysis.[35-37] Mortality reduction was difficult to prove in these trials. This is partly due to the fact that in a hospital participating in a trial with prehospital treatment, in-hospital treatment was also remarkably shorter than in hospitals not participating in such a program.[37] Table 2.4-1 gives the results of 6 trials randomising between pre- and in-hospital thrombolysis.[38]

Table 2.4-1. Trials randomising between pre- and in-hospital thrombolysis.[38]

Study	Thrombolytic agent	TTT; minutes, median, prehospital	TTT; minutes, median, in-hospital	Difference, minutes	In-hosp. mortality prehospital treatment	In-hosp. mortality in-hospital treatment
Castaigne 1989[41]	anistreplase	131	180	60	3/57 5.3%	3/43 7.0%
Roth 1990[39]	rt-PA	94 (36)*	137 (45)*	n.a.	4/72 5.6%	3/44 6.8%
Schofer 1990[40]	urokinase	85 (51)*	137 (50)*	n.a.	1/40 2.5%	2/38 5.3%
GREAT 1992[36]	anistreplase	101	240	130	11/163 6.7%	17/148 11.5%
MITI 1993[37]	rt-PA	77	110	33	10/175 5.7%	15/175 8.6%
EMIP 1993[35]	anistreplase	130	190	55	251/2750 9.1%	284/2719 10.4%

TTT=time to treatment, n.a. = not available, in-hosp. = in-hospital
* Mean with standard error between brackets

Inclusion criteria in these trials were similar and restricted to symptoms and signs of acute myocardial infarction, with the exception of the GREAT trial,[36] for which ECG-diagnosis was not a prerequisite. In the GREAT[36], EMIP[35] and MITI[37] trial, patients were randomised to pre- or inhospitally treatment. In the Roth[39], Schofer[40] and Castaigne[41] studies prehospital treated patients were randomly compared with in-hospital treated patients without randomisation.
The time difference between the prehospital group (104 minutes) and the in-hospital group (162 minutes) is about 60 minutes (p=0.007), and without the GREAT study, being conducted in the remote county of Aberdeenshire, 45 minutes (p=0.01). None of the studies showed a statistically significant difference in favour of prehospital thrombolysis. GREAT and MITI measured 1-year mortality, only the GREAT study reported 5-year mortality data. All studies favoured prehospital thrombolysis but only in the GREAT study, with the largest time interval between pre-and in-hospital thrombolysis, this reached statistically significant differences in mortality. Pooling the results favoured prehospital thrombolysis,[38] lowering the risk of all-cause hospital mortality with 17%. Taking all early treated patients together, pre-or in-hospitally treated, the MITI study showed that a statistically significant reduction on the combined outcome of hospital mortality, ejection fraction and infarct size was seen in patients treated within 70 minutes of onset of symptoms. The absolute risk reduction of 2% compared to in-hospital treatment translates into 1 life saved for every 62 patients treated.

2.5 The Golden Hour of thrombolysis

In 1994 the Fibrinolytic Therapy Trialists Collaborative Group (FTT) published a meta-analysis of 9 trials, randomising more than 1000 patients between fibrinolysis and control, in order to evaluate the effects of treatment on mortality and morbidity (table 2.5-1).[42]

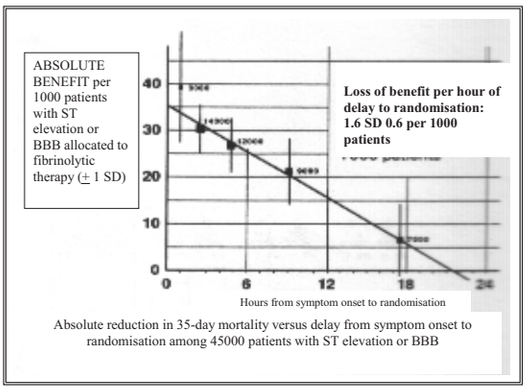
Table 2.5-1. Nine trials randomising between fibrinolytic therapy and control.[42]

	GISSI-1 n=11802	ISAM n=1741	AIMS n=1254	ISIS-2 n=17187	ASSET n=5012	USIM n=2201	ISIS-3 n=9158	EMERAS n=4534	LATE n=5711
Fibrinolysis	SK 1.5 MU	SK 1.5 MU	APSAC 30 U	SK 1.5 MU	rt-PA 100 mg	UK 1 MU x 2	* SK 1.5 MU * rt-PA 0.6 MU/kg * APSAC	SK 1.5 MU	rt-PA 100 mg
Control	open	placebo	placebo	placebo	placebo	open	open	placebo	placebo
Aspirin	no	yes	no	yes	no	no	yes	yes	yes
Heparin	no	yes	no	yes	yes	yes	yes	no	yes
Period	'84-'85	'82-'85	'85-'87	'85-'87	'86-'88	'86-'88	'89-'91	'88-'91	'89-'92

SK=streptokinase; APSAC=anistreplase; UK=urokinase; rt-PA=recombinant tissue plasminogen activator.

In total 58,600 patients were included. Most of these patients had ST-segment elevation on the presenting ECG (68%), but it is important to note that not always ECG-abnormalities were needed for diagnosis (5% had near-normal ECG s). There was an 18% reduction of 35-day mortality in the thrombolytic group, which was highly significant. Risk reduction was greatest in patients with ST elevation (21%), especially with ST-segment elevation in the anterior leads (25%). The earlier a patient was treated, the greater the mortality reduction (fig. 2.5-1). Regression analysis of the absolute benefit versus the mean delay from symptom onset indicated an approximately straight line relationship, as can be seen from figure 2.5-1, and pointed out that every additional hour of treatment delay was associated with a reduction in benefit by about 1.6 lives per 1000 patients treated.

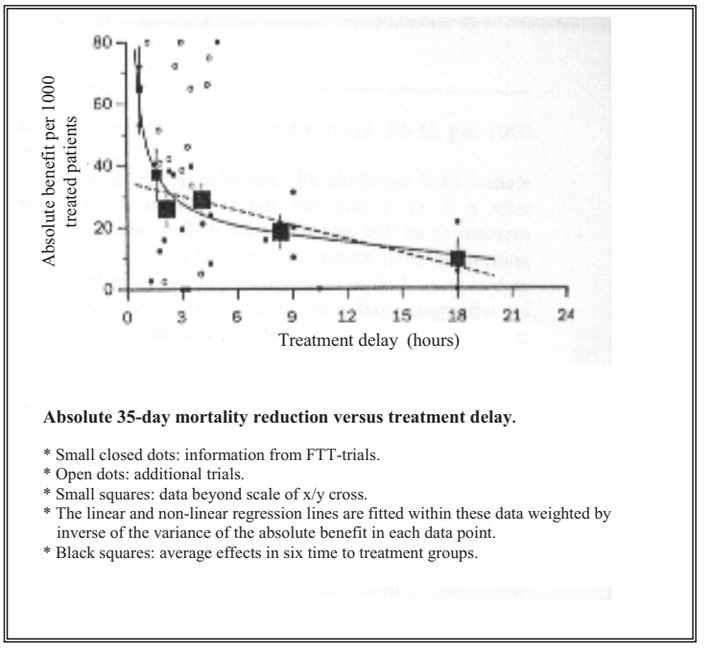
Fig 2.5-1. Mortality reduction at 35 days and time to treatment. From[40] with permission



BBB = bundle branch block

In 1996 Boersma, helped by the Reimer & Jennings and Bergmann experiments, investigated early fibrinolysis in further detail.[43] The FTT authors did not find an additional treatment benefit in the patients treated within 0-1 hours, but this could be explained by not including trials with small numbers of patients, for instance those trials with a prehospital strategy and, thus, early treated patients. So, in the Boersma analysis, smaller trials consisting of at least 100 patients, some with prehospital treated patients, were included. Furthermore, contrary to the FTT-analysis, both linear and non-linear regression analyses were used to test the relation between benefit and early treatment. In the 22 trials, only 11% of patients were treated within 2 hours of symptom onset.

Fig. 2.5-2. Best-fit curve relating mortality reduction and time to treatment. From [43] with permission from Elsevier Science (Lancet 1996;348:771-775).



Absolute 35-day mortality reduction versus treatment delay.

* Small closed dots: information from FTT-trials.
* Open dots: additional trials.
* Small squares: data beyond scale of x/y cross.
* The linear and non-linear regression lines are fitted within these data weighted by inverse of the variance of the absolute benefit in each data point.
* Black squares: average effects in six time to treatment groups.

Figure 2.5-2 gives the results of their best-fit curve, whereby the non-linear regression curve resulted in a closer match than the linear regression analysis. Very early reperfusion of the occluded coronary artery, for instance within 30 minutes, may lead to full recovery of ischaemic tissue and, thus, to prevention

of necrosis. The concept of aborted myocardial infarction, explained in section 2.1 of this overview, thus comes into view. The advantage of very early therapy in the prehospital studies is much larger than the effect of 1 hour earlier therapy as reported in the FTT-analysis. Patients with a shorter treatment delay, however, may well differ from later presenting patients: e.g. larger infarcts, younger patients, men rather than women. Boersma concludes that the assessment of prehospital treatment is likely to be better by dividing all patients (prehospital and hospital) in an early and a late treatment group, rather than comparing prehospital with in-hospital patients. Comparing only in-hospital treated patients yields too few patients to compile an early treatment group, as only an average of 6% of in-hospitally treated patients are treated within 1 hour.[43] Prehospital thrombolysis is thus the only way to compile an 1- and 2-hour treatment group large enough to make such an assessment possible.

2.6 Time to reperfusion in primary angioplasty

Besides early administration of therapy, achieving complete reperfusion of the infarct-related artery is another important predictor of improved outcome. In angiographic studies, the degree of reperfusion is expressed in TIMI-flow at 90 minutes after initiation of therapy. TIMI grade 0 means no reperfusion, grade 1 penetration of contrast without reperfusion, grade 2 partial and grade 3 complete reperfusion.[44] Many studies have shown that TIMI-3 flow 90 minutes after initiation of thrombolytic therapy is associated with the best mortality reduction.[45] However, using thrombolytic therapy, 90 minutes TIMI-3 flow is established within that time frame in 60% of patients with frontloaded rt-PA.[2] Primary angioplasty is expected to achieve TIMI-3 flow in a higher percentage of patients and so could result in a better clinical outcome. But arranging mechanical opening of an occluded coronary artery after presentation a patient in the hospital usually costs considerable time. A review of 10 randomized studies of primary angioplasty versus various regimens of fibrinolysis showed that the time to angioplasty was 17 to 59 minutes later than the time to treatment using thrombolytic therapy.[2] The largest of those studies, GUSTO-IIb, had 565 patients randomized to primary angioplasty and 573 patients randomized to fibrinolysis. After a time to presentation of 1.9 and 1.8 hours respec-

tively, the time to treatment was 50 minutes longer in the angioplasty group. The endpoints of death, re-infarction and nonfatal stroke were significantly lower in the primary angioplasty group (9.6% versus 13.6%) compared to fibrinolysis, but were primarily lower because of the difference in re-infarction.[46] In these randomized studies, mortality reduction, re-infarction rate and hemorrhagic stroke favored primary angioplasty, although the short-term benefits were more favorable than the endpoints at follow-up. Furthermore, many of these trials were performed in the early nineties, when door-to-needle time in thrombolysis exceeded 40 minutes and patients randomized to fibrinolysis were treated late. Treatment of either fibrinolysis or angioplasty in the real world showed an average time-to-hospital admission of 2.5 hours in both groups, none of the patients treated within one hour and only a few within two hours, with no mortality benefit for primary angioplasty.[47] In the National Registry of Myocardial Infarction with 27,080 patients treated with primary angioplasty the median time from onset of chest pain to hospital arrival was 1.6 hours and the median time from onset to angioplasty 3.9 hours. The multivariate-adjusted odds of mortality was 40% to 60% higher in patients with a door-to-balloon time longer than 2 hours, which was in 53% of patients.[48] In contrary with thrombolysis where mortality increases with time to treatment, mortality with primary angioplasty and door-to-balloon times longer than 2 hours does not increase. This can be explained by the high rate of reperfusion established with angioplasty in late presenting patients, whereas thrombolysis will have less effect in realizing patency.[48] Assuming that the benefits of reperfusion are independent of the way it is established, time to and completeness of reperfusion, the rate of stroke and of re-infarction together with experience of the cardiologist performing the angioplasty can explain the favorable outcome of angioplasty.[49] Focusing on time to reperfusion: A recently presented study randomizing 840 patients with prehospital thrombolysis versus primary angioplasty revealed no significant difference (death, non-fatal reinfarction and non-fatal disabling stroke) between both treatment arms, although the need for urgent angioplasty because of re-infarction was higher in the thrombolysis group.[6] Another study combining prehospital thrombolysis and standby rescue angioplasty in 170 patients resulted in 91% TIMI-3 patency, with time-to-thrombolysis in 151 $\pm$ 61 minutes and rescue angioplasty performed in 50 patients (29%). Time to TIMI-3 flow in these group was 264 $\pm$ 78 minutes. This

group was compared with 170 matched patients treated with primary angioplasty; the comparison resulted in the same TIMI-3 patency of 91%, and a comparable 30 day mortality of 4.1% in the prehospital thrombolysis group and 4.7% in the primary angioplasty group, with the time to TIMI-3 flow of the primary angioplasty group of 232 $\pm$ 94 minutes.[50] In other words, if the time to reperfusion using angioplasty or thrombolysis becomes similar, it is expected that the benefit of angioplasty becomes comparable to the benefit of thrombolysis.[51] In the current guidelines primary angioplasty is advocated in patients with acute ST-segment elevation myocardial infarction if can be performed within 90 — 120 minutes after presentation by skilled operators in high-volume centers. Perhaps the best of both worlds should be implemented: early treatment using prehospital thrombolysis combined with establishing TIMI-3 flow with (rescue)-angioplasty.[50,52]

2.7 Summary

Acute ST elevation myocardial infarction, caused by a thrombotic occlusion of a coronary artery, results in myocardial cell death, occurring as a wavefront from endocardial tissue to epicardial tissue. The amount of cell death is dependent of the duration of coronary artery occlusion, cell death being apparent after 40 minutes in experiments with dogs. The viability of myocardial cells in the dog experiment is reflected by many trials using thrombolytic drugs, where the mortality is reduced when treatment is started early after onset of symptoms. Meta-analysis of randomized trials showed that the gain from this treatment is optimal if it is started in the first hour, the Golden Hour. However, in-hospital only few patients can be treated within that hour, so attention has been drawn to prehospital treatment. Prehospital thrombolysis leads to a time gain of 30-60 minutes and saves about 1 extra life in 60 patients treated in comparison to in-hospital therapy. The literature of primary angioplasty is also emphasizing early treatment, certainly within 2 hours after presentation at the hospital. Thus, the importance of early therapy cannot be exaggerated and it seems from the literature that prehospital initiated triage and thrombolysis is one of the means to accomplish this.

2.8 References

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CHAPTER 3

STUDY OF TIME INTERVALS IN MYOCARDIAL ISCHAEMIC SYNDROMES (STIMIS)

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Adapted from *Netherlands Heart Journal 1998;5: 23-30.*

3.1 Abstract

In the STIMIS-study the various points in time of every event between onset of chest pain and completed hospital admission were assessed in 1,152 patients with chest pain of possible cardiac origin. This study was part of the Nijmegen Home Thrombolysis Program. Of these patients 200 were actually treated with thrombolytic therapy: 141 at home and 59 after hospital arrival. After final analysis, 393 patients proved to have myocardial infarction. In comparison with the whole group of patients with chest pain, the time points of every event occurred earlier in patients with myocardial infarction. There was a median time interval of 89 minutes between onset of symptoms and treatment in patients treated prehospitally, and 152 minutes in patients treated in-hospitally. Of the prehospital thrombolysis group 28% of the patients and of the hospital thrombolysis group no patients were treated within one hour. Within two hours these values were 65 and 25%, respectively.

3.2 Introduction

Timely reperfusion of an occluded coronary artery, salvages left ventricular function,[1-3] and reduces mortality risk in patients with acute myocardial infarction.[4-9] Every hour thrombolytic therapy can be given earlier 23 more lives are saved per 1000 treated patients; if thrombolytic therapy is administered within the first hour of onset of symptoms, even 65 to 69 lives per 1000 treated patients can be saved.[10,11]

From the early years of thrombolysis on, the two Nijmegen hospitals have spent much energy in shortening the door-to-needle time. This was 83 minutes in 1985, and reduced to 48 minutes in 1995.

To shorten the treatment intervals, a prehospital thrombolysis project was started in 1987 (figure 3.2-1). At the start of the project, the general practitioners feared the time delays of ECG-transmission, ECG-interpretation and preparation of thrombolytic treatment at the patient s home, and thus of the actual time gain which could be reached. The STIMIS (Study of Time Intervals in Myocardial Ischaemic Syndromes) study entailed a detailed measurement of all time intervals of diagnosis and treatment of patients with a suspected acute coronary syndrome. The STIMIS-study is a joint project of the regional ambulance service, the general practitioners and the Nijmegen cardiologists.

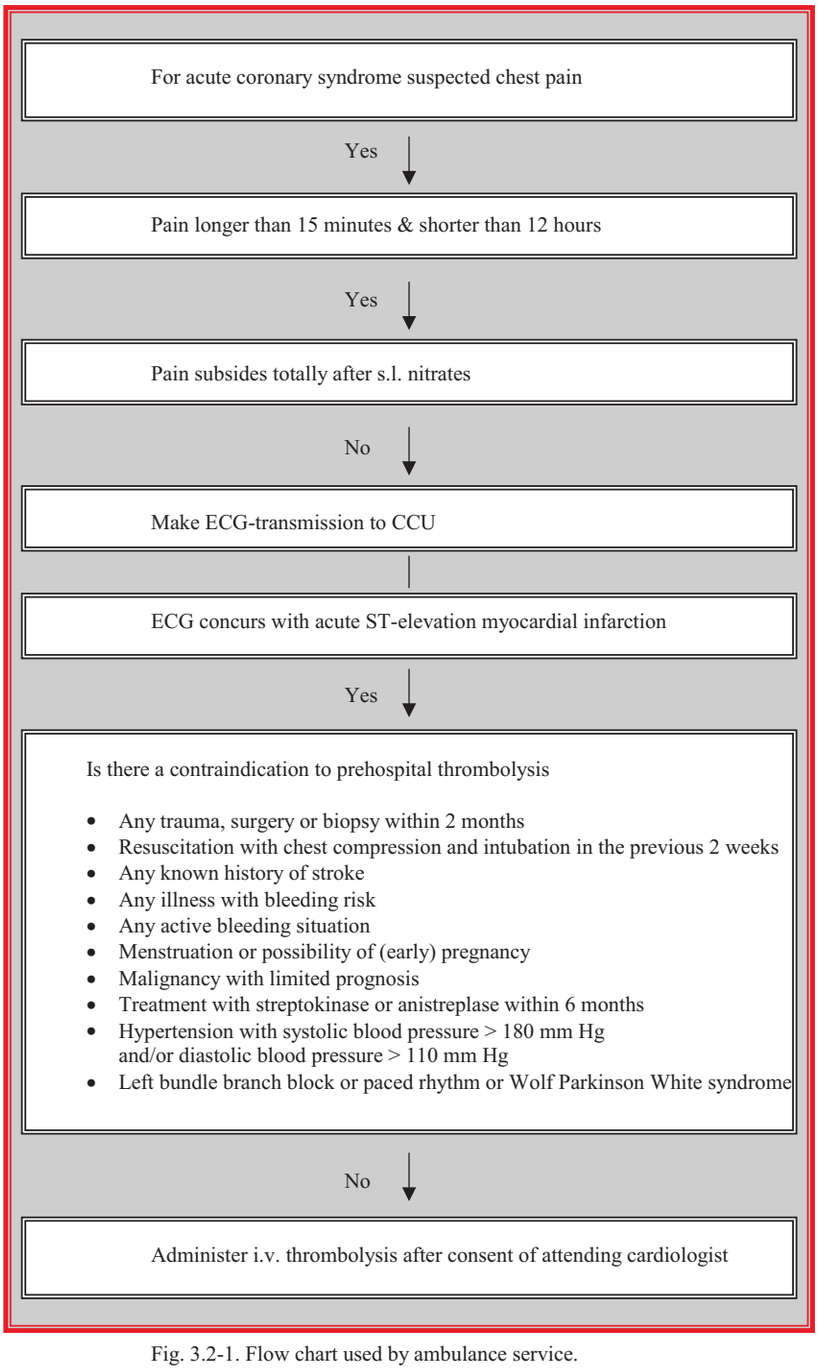
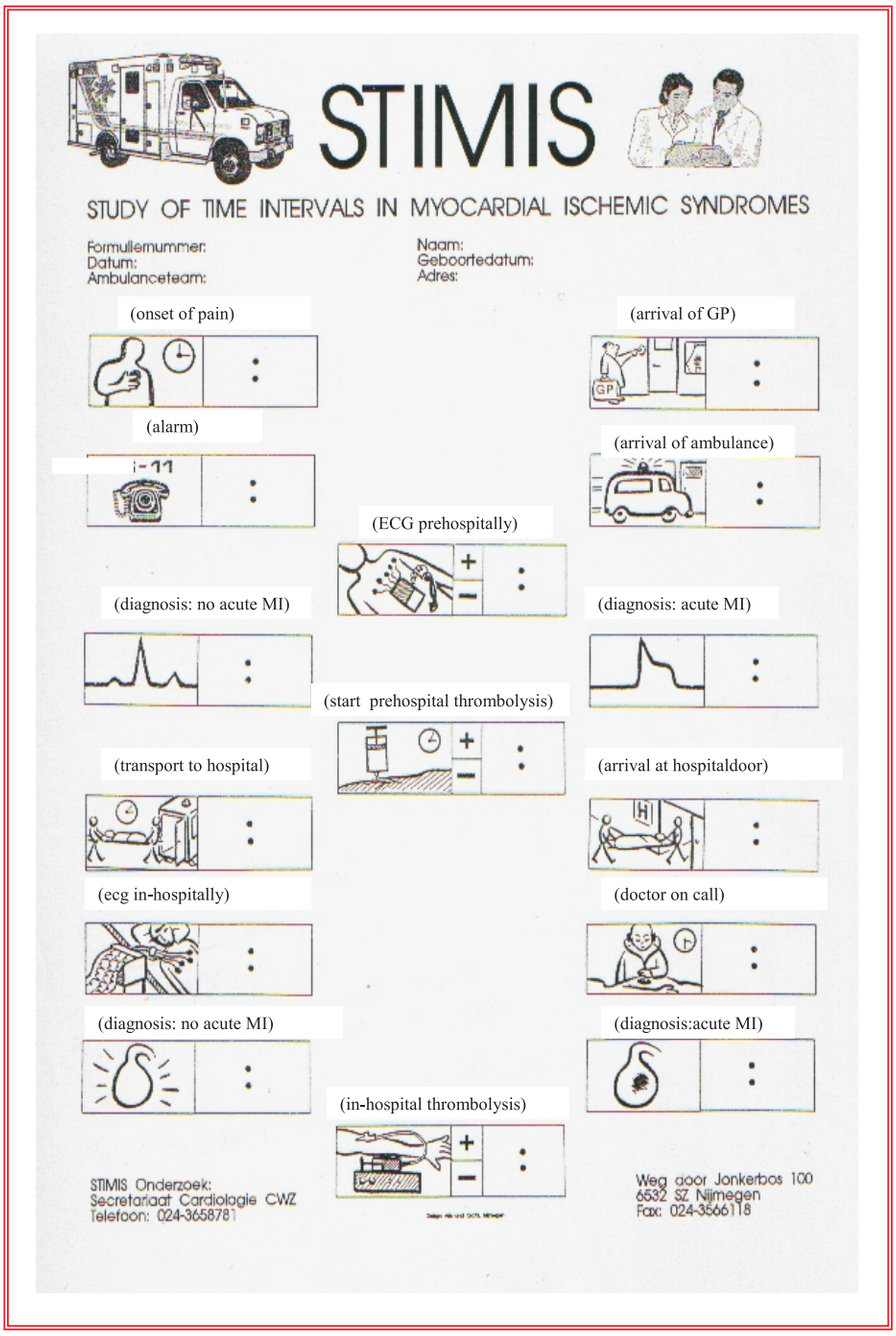


Fig. 3.2-1. Flow chart used by ambulance service.

3.3 Patients and methods

Various time intervals of treatment for acute myocardial infarction in the Nijmegen region were carefully collected to assess the time gain of prehospital treatment, from the onset of pain to administering treatment pre- or in-hospitally. The registration of time intervals started at October 1, 1995 and ended Augustus 1, 1997, and included all patients complaining of characteristic chest pain. Time intervals were noted by the ambulance service, by attending CCU-doctors and by nurses of the cardiac care units of the two Nijmegen hospitals. To facilitate the registration, a portfolio was used with a mounted digital clock, containing a specially designed form on which details of various time intervals could be noted (figure 3.3-1). The general practitioner or ambulance staff regarded characteristic chest pain of more than 30 minutes and less than 6 hours duration an indication for starting the procedure, regardless of the definitive diagnosis. An ECG was made by the ambulance staff, and transmitted to the CCU of the Canisius-Wilhelmina Hospital using an analog transtelephonic transmission method. If the transmitted ECG showed signs of acute myocardial infarction and a checklist did not reveal a contra-indication for thrombolytic therapy, patients were treated with 30 mg of anistreplase before transport to one of the 2 Nijmegen hospitals (Canisius-Wilhelmina Hospital and University Medical Center St Radboud).
Statistical test used were t-test for numbers, Wilcoxon test for time intervals and Chi-square test for percentages.

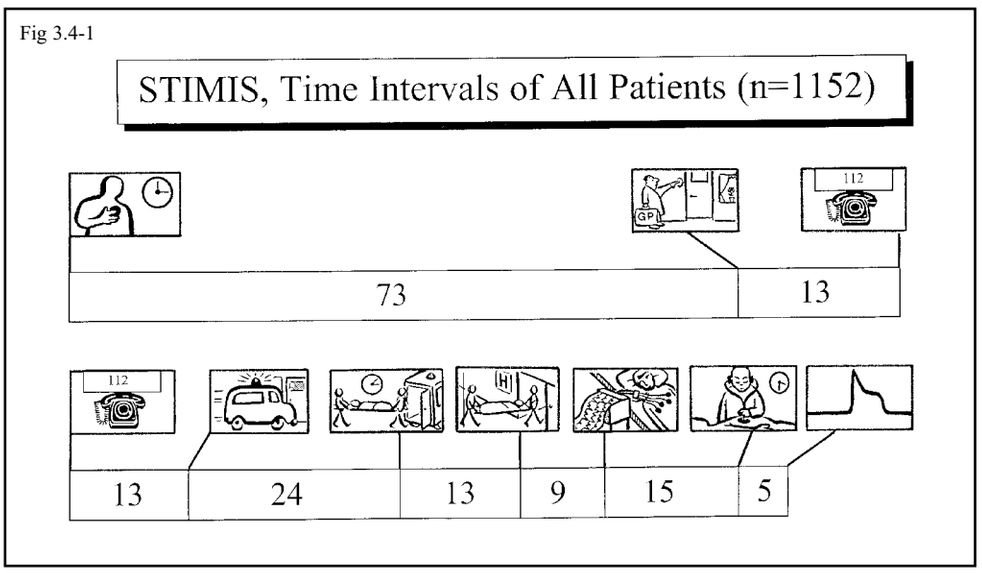
Fig 3.3-1. Form to note various time intervals concerning patients with chest pain



3.4 Results

A total of 1,152 patients were included in the study. After final analysis, 393 patients proved to have an established myocardial infarction. Figure 3.4-1 presents the time intervals of all 1,152 patients, in minutes and in median values. Between onset of symptoms and arrival of the general practitioner 73 minutes elapsed; the general practitioner took 13 minutes to assess the situation, followed by the arrival of the ambulance by 13 minutes. The ambulance staff took 24 minutes to stabilise and connect the patient to the monitor and to transmit the ECG. It took 13 minutes to transport the patient to one of the two Nijmegen hospitals, and 9 minutes to produce an ECG in the hospital. Fifteen minutes later the hospital doctor arrived and used 5 minutes to make a diagnosis.

Fig 3.4-1

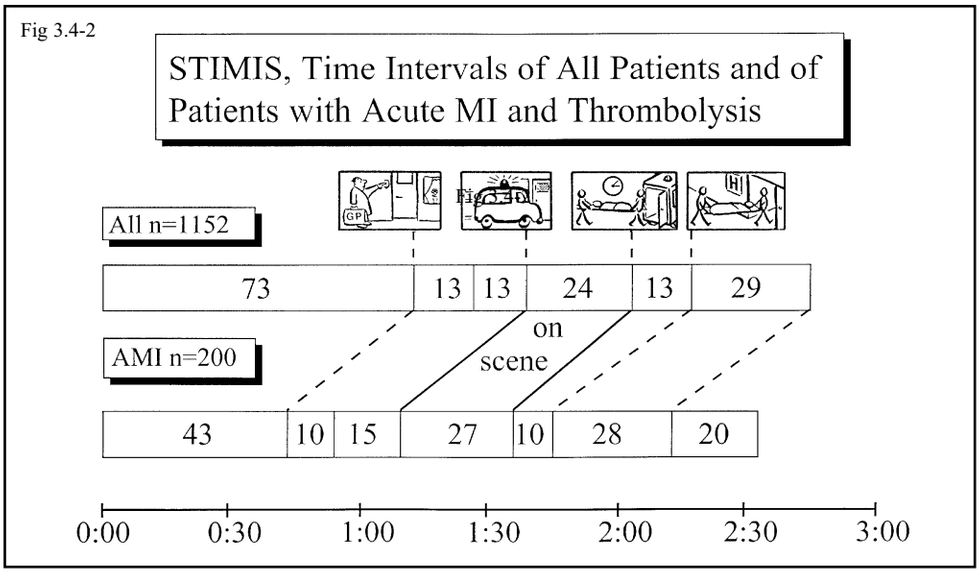


Time intervals of 200 patients with acute ST-elevation myocardial infarction, compared to all 1152 patients (fig 3.4-2).

The process of alarming the general practitioner was considerably and significantly faster in the case of an acute ST-segment elevation myocardial infarction (43 minutes versus 73 minutes; $p<0.0001$, Wilcoxon-test). The on-scene time is longer in patients with myocardial infarction, probably because of the admin-

istration of the thrombolytic drug. The difference is, however, not significant from no thrombolysis. The diagnostic process in hospital is faster in the patients having acute myocardial infarction compared to all patients with chest pain.

Fig 3.4-2

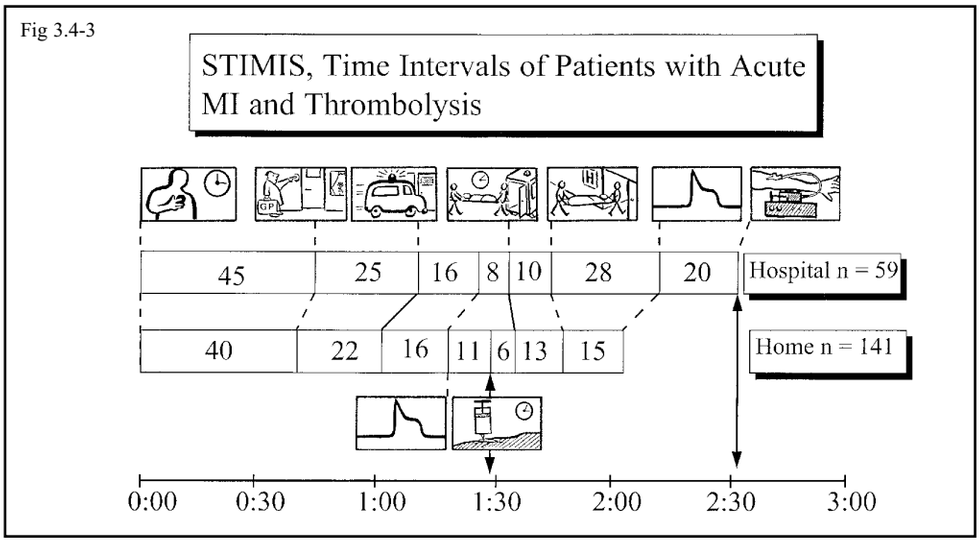


Time intervals of 200 patients with acute ST-segment elevation myocardial infarction; 141 treated prehospitally and 59 treated inhospitally (fig 3.4-3).

Figure 3.4-3 shows the time intervals of patients treated prehospitally versus inhospitally. The on scene time of the ambulance service was longer in the patients treated prehospitally (33 versus 24 minutes). The time between arrival of the ambulance and prehospital diagnosis is 16 minutes in both groups; the difference in on-scene time is explained by the extra 11 minutes between prehospital diagnosis and administration of the thrombolytic drug ($p<0.05$, Chi-square test). There was a median time interval of 89 minutes between onset of symptoms and treatment in patients treated prehospitally. In-hospital confirmation of the diagnosis of the patients treated prehospital is faster than of the patients treated inhospital (15 versus 28 minutes). Between hospital diagnosis and thrombolysis another 20 minutes elapse, adding up to 152 minutes between onset of symptoms and treatment in patients treated inhospitally. The total ST-segment deviation of the prehospital treated group of 1.8 mV is significantly

greater than those of the in-hospital group of 1.0 mV.

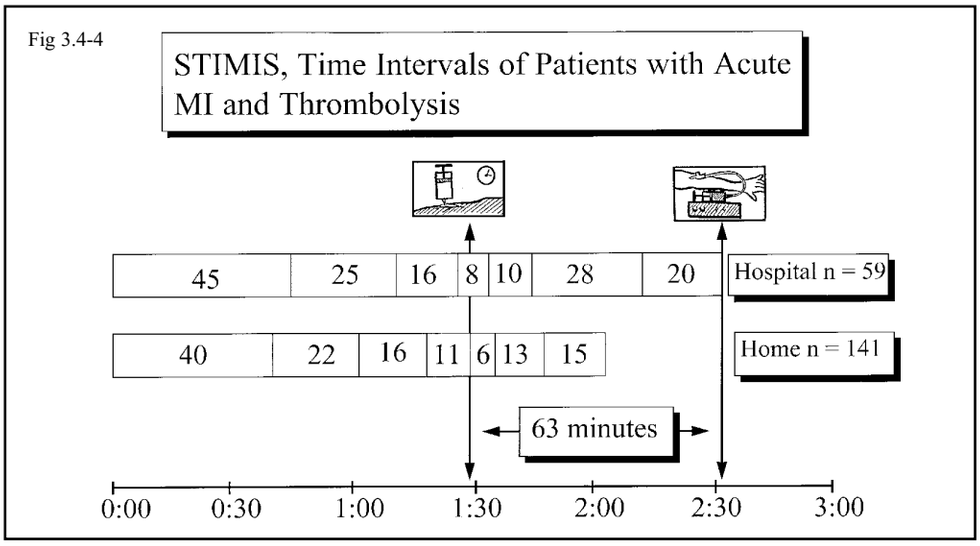
Fig 3.4-3



Difference in time between prehospital thrombolytic therapy and in-hospital thrombolysis (fig 3.4-4).

There was a 63 minutes time gain by treating patients prehospitally. If corrected for the fact that the ambulance service arrived 8 minutes earlier in the prehospital treated patients, the time gain was 55 minutes.

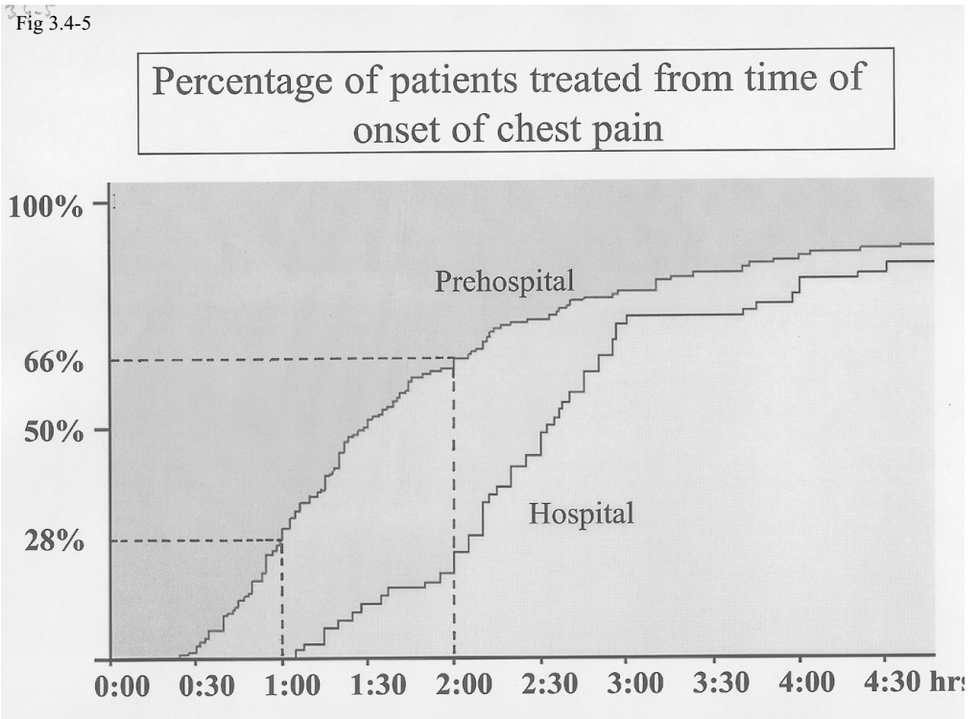
Fig 3.4-4



Percentage of patients treated prehospitally or in hospitally as function of time to treatment (fig 3.4-5).

The earliest patient treated prehospitally was within 25 minutes after onset of pain, while the earliest in-hospital patient could be treated within 65 minutes. Within the first hour 40 patients were treated using prehospital treatment (28%), and within the second hour 92 patients (65%). None of the in-hospital patients were treated within one hour and within 2 hours only 15 patients (25%); this difference is statistically significant ($p<0.01$).

Fig 3.4-5



3.5 Discussion

Patients in the Nijmegen region with chest pain sought medical help fairly fast after onset of symptoms: 73 minutes. In the case of acute myocardial infarction this interval is reduced to about 40 minutes. Apparently, both patient and general practitioner clearly recognized the pressing need for medical help. This is a selection, because this study included only those patients for whom the general practitioner called the ambulance service immediately. In less urgent cases possibly more time is spent at the patient s home.[12] The time of the ambulance to arrive at the patient was within the limits of 15 minutes as determined by the Dutch health authorities.

The ambulance staff needed 24 minutes to prepare the patient, to introduce him or herself, to consult the general practitioner, to connect the patient to the portable monitor and to register the ECG. The administration of the medication was fast: the total on-scene time was only 9 minutes longer in a prehospital treated patient while the total on-scene time of 33 minutes concurs with the 26 minutes of other studies.[13] The transport time of 13 minutes to the hospital concurs with the 13 minutes of Kereiakes registration.[14] At arrival at the cardiac care unit patients are immediately attended by the CCU-staff, but the arrival of the hospital physician took a precious 15 minutes. After a fast diagnosis of 5 minutes it took 20 minutes before the treatment was started.

The total door to needle time of 48 minutes was 12 minutes longer than the 36 minutes from the REPAIR-trial, although decidedly shorter than the 83 minutes from the early days of thrombolysis and comparable with the 49 minutes in a fast-track strategy.[15] Only Chamberlain had better results of 25 minutes.[16]

Prehospital treatment of acute myocardial infarction gained 63 minutes. Subtracting 8 minutes from the ambulance service arriving earlier at this group the time gain of 55 minutes concurs with the EMIP-study.[17] The Nijmegen registration can be compared with other time studies, both in rural and urban areas.[18,19]

Prehospital thrombolysis is limited to patients having chest pain of 6 hours or less duration. However, our survey did include in-hospital treated patients with chest pain of 24 hours duration, thus making the time gain artificially favorable. Excluding 7 patients with chest pain longer than 6 hours resulted in the median door-to-needle time in this group to be 47 minutes instead of 48 minutes.

With prehospital thrombolysis 28% of patients could be treated within one hour and 65% within 2 hours. Administering fibrinolytic therapy in the hospital is associated with no patient treated within the golden hour and only 25% within 2 hours. The MITI- and the REPAIR-study came to the same conclusion of only 1% of patients treated within 1 hour.[18,20] However, using a prehospital strategy the number of patients treated within 1 hour varied between 13% in the GREAT-study[11] to 40% in the REPAIR-study.[20]

3.6 Conclusion

The STIMIS-registration was set up to register time intervals in our own Nijmegen hospitals, to assess the time that could be gained by performing prehospital thrombolysis and to compare the results with data from the literature. On the one hand insight is gained of the time intervals involved, on the other hand shortcomings were revealed. With prehospital thrombolysis in the Nijmegen one quarter of patients can be treated within 1 hour and two thirds within 2 hours, which is significantly better than the results of in-hospital treatment.
The STIMIS-registration confirmed other studies, that only with prehospital thrombolysis it is possible to treat a considerable percentage of patients within the Golden Hour. Registrations such as these have been done in other cities of the area, and will be of great importance in the triage and treatment with prehospital treatment or primary angioplasty of patients with acute coronary syndromes.

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Chapter 4

Registration of symptom onset-to door and door-to-needle times in 4 hospitals outside the Nijmegen region

Potential impact of a prehospital triage protocol

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4.1 Abstract

Background: To facilitate discussions about the need for prehospital thrombolysis in regions other than Nijmegen, where such a strategy already exists, in-hospital time intervals of diagnosis and treatment of patients with chest pain must be collected and an estimation of percentages of patients that can be treated within 2 hours with this strategy must be made.

Patients and methods: In 4 regional hospitals around the city of Nijmegen time intervals were noted on a special form. To calculate the time gain prehospital treatment could have provided in the 4 regions to the median time from onset of pain to arrival of the ambulance 27 minutes was added, which is the time it takes in Nijmegen to diagnose and treat the patient in the prehospital approach.

Results: Door-to-needle times in the 4 regions varied between 39 and 50 minutes and are comparable with the 48 minutes of in-hospital treatment in Nijmegen. Total time to treatment varied between 145 and 167 minutes. If a prehospital strategy had been present, there would have been a time gain in the 4 regions varying between 32 and 51 minutes, resulting in 55% patients treated within 2 hours instead of the current 25%.

Conclusion: With a prehospital strategy the 4 regions could reduce the time to treatment, resulting in doubling the number of patients treated within 2 hours.

4.2 Introduction

Prehospital thrombolysis of acute myocardial infarction in the city of Nijmegen results in a median time gain of about one hour, resulting in 28% of patients treated within one hour after onset of pain.[1] Physicians in other regions however, are reluctant to start a prehospital strategy for the treatment of acute myocardial infarction. Many physicians are not aware of the long door-to-needle time in their own institutions. Health authorities and general practitioners do not realize that as soon a patient has entered a hospital, diagnosis and treatment take considerable time.
To facilitate discussions about the need for prehospital thrombolysis in cities other than Nijmegen, the cardiology departments and ambulance services of 4 other regions agreed to participate in a registration of the in-hospital time intervals of diagnosing and treating patients with chest pain. The aim of this study was to obtain insight in the percentage of patients treated within two hours after onset of pain. Furthermore, using on-scene times of prehospital treatment and diagnosis in Nijmegen, an estimation can be made of the time gain prehospital treatment could provide in those regions.

4.3 Patients and methods

All patients with chest pain suggestive of acute coronary syndrome were included in the registration. The same form was used as in the STIMIS-registration in Nijmegen,[1] with an extra box to enter the region and city the patient was referred to. All time intervals were entered in an Excel-database, and average and median time intervals were calculated. To calculate the point in time where prehospital treatment could have been administered provided in the 4 regions, 27 minutes was added to the moment of ambulance arrival. Twenty-seven minutes is the on-scene time it takes in Nijmegen to diagnose and treat the patient in the prehospital strategy.

4.4 Results

The registration was made from August 1, 1997 till July 30, 1998. In Arnhem 375 patients were registered with chest pain, of whom 120 patients had a con-

firmed acute ST elevation myocardial infarction. In Boxmeer 94 patients were registered, from whom 41 had acute ST elevation myocardial infarction confirmed. In Deventer these numbers were 98 and 29 respectively, and in Zevenaar 15 with confirmed ST elevation myocardial infarctions in all.

Table 4.4-1. Summary of time intervals and time from onset to treatment, median, minutes

	Nijmegen n=1,152	Arnhem n=375	Boxmeer n=94	Deventer n=98	Zevenaar n=15
Door-to-needle	48	50	39	50	47
Time to treatment	153	166	145	167	150

Table 4.4-1 gives the summary of the door-to-needle time and the time to treatment while table 4.4-2 gives the percentages of patients, which could be treated within one, two, three hours or later than that.

Table 4.4-2. Percentages of patients actually treated within one, two and three hours.

	Nijmegen		Arnhem	Boxmeer	Deventer	Zevenaar
	PH	IH				
TTT < 1 hour	28%	0%	0%	0%	8%	0%
TTT < 2 hours	65%	25%	17%	45%	8%	20%
TTT < 3 hours	80%	70%	54%	91%	67%	47%
TTT $\geq$ 3 hours	20%	30%	43%	9%	33%	47%

PH=prehospital treatment.
IH=in-hospital treatment.
TTT=time to treatment

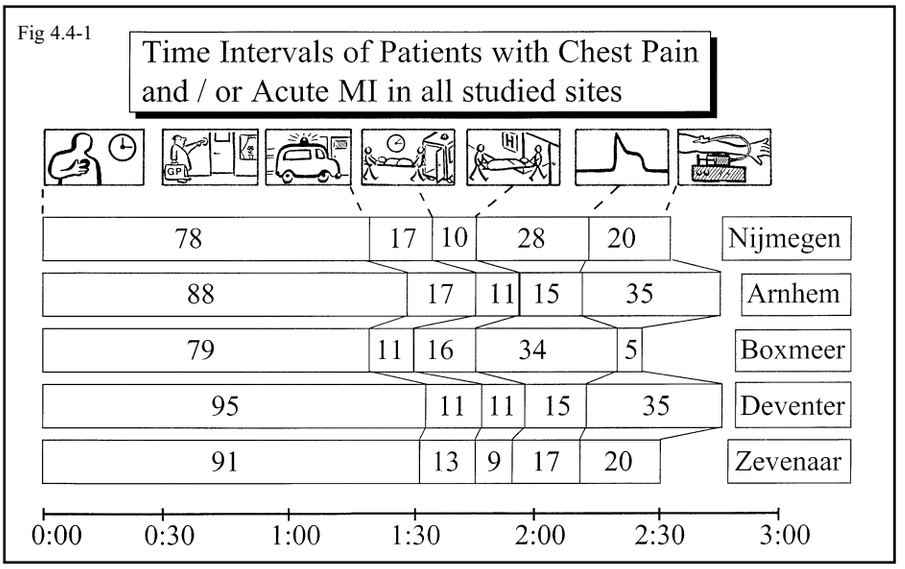
Table 4.4-3 gives the time to treatment together with the calculated time to treatment if a prehospital program would have been present.

Table 4.4-3. Time gain calculated from the Nijmegen time intervals, if a prehospital strategy would have been present.

	Time to treatment hospital therapy	Time to treatment prehospital therapy	Calculated time to treatment if a prehospital strategy would have been present	Calculated time gain if a prehospital strategy would have been present
Nijmegen	153	91	---	---
Arnhem	166	---	115	51
Boxmeer	145	---	106	39
Deventer	167	---	122	45
Zevenaar	150	---	115	32

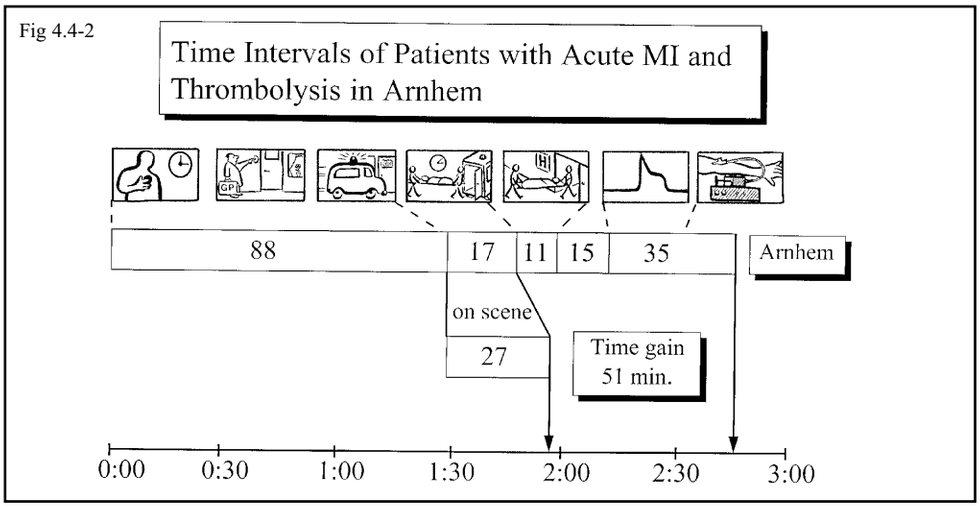
Figure 4.4-1 gives the results of the time intervals of patients with acute myocardial infarction of all sites. The door to needle time varies from 39 minutes in Boxmeer to 50 minutes in Deventer and Arnhem, and seems comparable to the 48 minutes in the Nijmegen hospitals.

Fig 4.4-1



In figure 4.4-2 Arnhem is chosen as an example to show the time gain that could be achieved by performing prehospital thrombolysis in Arnhem, starting from the principle that an on-scene time of 27 minutes for prehospital treatment would be the same in Arnhem as it is in Nijmegen.

Fig 4.4-2



The same calculation can be done in other sites (figure 4.4-3), resulting in an estimation of 55% of patients treated within 2 hours instead of about 25% using in-hospital treatment (table 4.4-4).

Fig 4.4-3

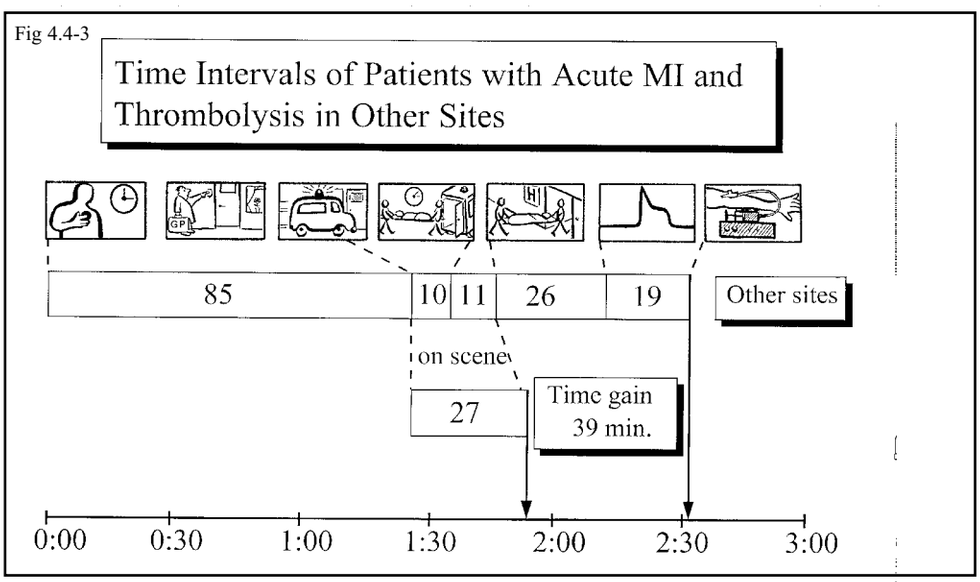


Table 4.4-4. Percentage of patients treated within 2 hours if a prehospital program in other sites would have been started.

Site		
Nijmegen	Prehospital thrombolysis	66%
Other sites	Potential prehospital thrombolysis	55%

4.5 Discussion

This registration suggests, that implementation of a prehospital thrombolysis program may shorten the time to treatment of acute ST elevation myocardial infarction up to 50 minutes. This concurs with time gains from the literature of prehospital treatment, which varies between 33 minutes in a large US city dedicated to early treatment and 130 minutes in a Scottish rural region. (table 4.5-1). [1-9]

Table 4.5-1. Mean time gain of prehospital treatment according to the literature.

Year of publication	Author	Number of patients	Mean prehospital TTT	Mean in-hospital TTT	Mean time gain
1989	McNeil[2]	57; HP=27; IH=30	119	187	68
1989	Castaigne[3]	93; PH=57; IH=36	131	180	60
1990	Barbash[4]	87; PH=43; IH=44	96	132	40
1990	Schofer[5]	78; PH=40; IH=38	85	137	43
1992	McAleer[6]	145; PH=43; IH=102	138	172	34
1993	EMIP[7]	5469; PH=2750; IH=2719	130	190	55
1994	GREAT[8]	311; PH=163; IH=148	101	240	130
1996	MITI[9]	360; PH=175; IH=185	77	110	33
1998	STIMIS[1]	200; PH=141; IH=59	89*	152*	63
2003	Adgey[11]	474; PH=257; IH=217	140*	240*	100

* Median values in stead of mean values, as is used in the text.

HP=prehospitally treated
IH=hospitally treated
TTT=time to treatment

It matches the 55 minutes of the EMIP study.[7] Although the importance of time to treatment in acute myocardial infarction has been stressed, there is no difference in time to treatment in the early years of prehospital thrombolysis[10] compared to this strategy in later years: the REPAIR-study, performed in Rotterdam from 1988 to 1993 described a mean time gain of 47 minutes with prehospital thrombolysis and a prehospital thrombolysis study performed around Belfast between 1998 and 2001 found a median time gain of 1.7 hours.[11]
In our study, time from pain onset till arrival of the ambulance varies between 78 minutes and 95 minutes. The on-scene time of the ambulance at the patient is decidedly longer in Nijmegen (with prehospital thrombolysis) than the 11 to 17 minutes in other regions, probably because of the time the transmission of the ECG and consultation with the CCU-physician took. Transport from the patient s home to the hospital is comparable in all cities and varied between 9 and 16 minutes. In all hospitals it took rather long to make a diagnosis: 15 to 34 minutes. Deciding the treatment and starting it is very short in one region (5 minutes) and can take 35 minutes in another. This means that the door-to-needle time varies between 37 and 52 minutes. This is in line with a report from an infarct registry, where from 1,302 patients with ST-segment elevation myocardial infarction a median door-to-needle time was measured of 52 minutes.[12] Furthermore, recent reports confirm that the door-to-needle time has been shortened from more than 1 hour in the early nineties to about 40 minutes, but that the goal of 30 minutes has not been reached.[13] Interestingly, patients developing acute myocardial infarction while being already admitted on a general ward had a median time to treatment of 120 minutes, according to an English survey, [14] more than 30 minutes longer than the prehospital treated patients in Nijmegen.[1] The median of 43 minutes between symptom onset and arrival of the GP concurs with the results of a study in Rotterdam, where 50% of patients with acute myocardial infarction sought medical help within a median of 45 minutes.[15]
The potential time gain by performing prehospital treatment is determined by two parameters: the on-scene time by the ambulance and the door-to-needle time in the hospitals. Although in some districts the time gain will be determined by the transport time, for instance when rural regions are involved,[8] it seems that in cities this does not seem to play a major role. More important is

the time it takes in the hospital to diagnose acute myocardial infarction, to decide to thrombolyse the patient and to prepare the drug. Because the time from symptom onset to thrombolytic treatment in the four cities is not markedly shorter than that of the large trials[16] (fig 4.4-1) or hospital audits[17], it is not expected that hospital delays will be reduced further. With nurse initiated thrombolysis the attending physician on call could safely be bypassed with a median door-to-needle time of 15 minutes; however, this scheme can only cover 66% of time,[5] and is thus inefficient compared to thrombolysis by ambulance staff.[17] Achieving a time to treatment of less than 2 hours in a substantial number of patients, for instance more than 50%, is only possible by treatment outside the hospital.

Study limitations

A limitation of our registration is that the time intervals of the diagnosis and in-hospital treatment of acute myocardial infarction, although meticulously noted by four hospitals, were compared to those of Nijmegen, where a prehospital strategy of thrombolysis is used, and where prehospital time intervals were noted by the ambulance staff. Yet, the time intervals between Nijmegen and the other regions are quite comparable.

4.6 Conclusion

Patients delay and hospital delay (door-to-needle time) are the most important factors in the delay of treatment of acute myocardial infarction. None of the hospitals managed to treat their patients as early as could be managed by prehospital treatment. If a prehospital strategy would be implemented in the four hospitals of the region, 55% of patients could be treated within 2 hours instead of current 25%.

Acknowledgements

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Chapter 5

Time from symptom onset to treatment and outcome in prehospital thrombolysis for acute ST elevation myocardial infarction

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5.1 Abstract

Background: Prehospital thrombolysis for acute ST elevation myocardial infarction shortened treatment by 60 minutes, and created a large patient group with treatment within 2 hours.

Objectives: We analyzed our database of patients prehospitally treated for acute ST elevation myocardial infarction in search of characteristics for a better outcome in the early treatment group.

Methods: From 1994 to 2000 a total of 475 patients were treated using prehospital administration of anistreplase (in 407 patients) or reteplase (in 68 patients) after diagnosis was confirmed with transtelephonic transmission of the ECG. There was no age limit. The patient data were divided into 2 groups: one treated within 2 hours after onset of pain (291 patients, 62%), and one treated later (171 patients, 37%). Thirty-day mortality, symptoms and clinical signs of heart failure were used as parameters of outcome. Both univariate and stepwise logistic regression analyses were used to test 30-day mortality against age, actual time to treatment, prior myocardial infarction, hypertension, diabetes, hyperlipidaemia, anterior myocardial infarction, Killip class, systolic blood pressure and heart rate at presentation.

Results: Overall 30-day mortality was 9.0%. Overall heart failure was in 16.4% of patients. Both mortality (5.5% vs. 15.2%, $p<0.02$) and heart failure (12.7% vs. 23.2%, $p<0.02$) were significantly lower in the early treatment group compared to the group treated late. Independent parameters showing a relation with 30-day mortality were age, time to treatment, hypertension and prior myocardial infarction. Age, time to treatment, hypertension and hyperlipidaemia were identified as predicting heart failure within the first 30 days.

Conclusion: In prehospital thrombolysis both 30-day mortality and heart failure were lower in an early treatment group of acute ST elevation myocardial infarction. Independent variables for 30-day mortality were age, hypertension, prior myocardial infarction and time to treatment and age, hypertension, hyperlipidaemia and time to treatment for independent predictors for heart failure.

5.2 Introduction

Many studies have shown that timing of thrombolytic therapy is a major determinant for the outcome of acute myocardial infarction. Shortening the time to treatment by 60 minutes means a decrease in mortality from 11.1 to 9.7%.[1] Administering thrombolysis within 1 hour after symptom onset should result in the best treatment outcome.[2] Although the importance of early thrombolysis is well established, registration of treatment delays have shown that only 10 % and not more than 25 % of patients are treated within 1 and 2 hours respectively.

To shorten the delay between coronary occlusion and thrombolytic treatment, we initiated a prehospital thrombolysis program, working in close cooperation with local general practitioners and ambulance service. Treatment could hereby be shortened by 60 minutes, a speed not matched in a comparable hospital group.[3] Furthermore, 25% of patients could be treated within 1 hour and 66 % within 2 hours, also not matched by hospital treatment. Based on these results, one would expect prehospital thrombolysis and early treatment to result in a better outcome than hospital treatment. A drawback may be that patients with larger infarcts tend to seek medical help early and confound early treatment with a less favorable prognosis. Moreover, those patients are more easily diagnosed because of decisive ECG changes, making them more favorable candidates for prehospital diagnosis and treatment than patients showing less distinctive ST-segment elevation.

We analyzed our database of prehospital treated patients in search for a better outcome in the early treatment group, using a stepwise logistic regression analysis.

5.3 Patients and methods

From 1994 to 2000 a total of 475 patients were treated for acute myocardial infarction using prehospital administration of anistreplase (in 407 patients) or reteplase (in 68 patients), after diagnosis was confirmed with transtelephonic transmission of the ECG. The general practitioner or ambulance staff regarded pain of more than 30 minutes and less than 6 hours duration, characteristic

of acute coronary syndrome not relieved by nitroglycerin, the reason for starting the procedure. There was no age limit. Aspirin was given orally. If the transmitted ECG showed more than 0.1 mV of ST-segment elevation in two anatomically contiguous leads or more than 0.2 mV in leads V_1 and V_2 and a checklist did not reveal contraindications for thrombolytic therapy, 30 mg of anistreplase or two times 10 MU of reteplase was given intravenously. Patients were transported to one of the two Nijmegen hospitals and details of the time intervals were noted on specially designed forms. Patients were divided into 2 groups: one with treatment within 2 hours after onset of pain, and one treated later than that. Thirty-day mortality and symptoms and clinical signs of heart failure were used as parameters of outcome. The diagnosis of heart failure was based on analysis of the patient hospital records and included mentioning of exertional dyspnea, orthopnea, nocturnal dyspnea, signs of peripheral edema or congested jugular veins plus the subsiding of symptoms following diuretic therapy. Patients with heart failure were classified according to Killip class I to IV. Rescue angioplasty was performed when pain and ECG abnormalities did not subside within 2 hours after start of treatment. The data were collected retrospectively. For comparison we choose the GUSTO-I time interval of 2 hours as the division point between early and late treatment.[4] Univariate contingency tables were analyzed with the uncorrected chi-square test. Stepwise logistic regression analysis was used to test 30-day mortality and heart failure against age (years), actual time to treatment (minutes), prior myocardial infarction, hypertension, diabetes, hyperlipidaemia, anterior myocardial infarction, Killip class, systolic blood pressure and heart rate at presentation. The level of significance used was 5%.

5.4 Results

Baseline characteristics

Table 5.4-1 gives the results of the baseline characteristics of 468 patients. Excluded were 7 patients (1.3%) who (1) did not have an increase in cardiac enzymes, and (2) had no dynamic ecg changes characteristic of abortion of myocardial infarction[3] and (3) from whom, in retrospect, the history and electrocardiograms suggested no myocardial ischemia.

A total of 98 patients (20.9%) were treated within one hour, 291 (62.2%) within 2 hours, and 171 (36.5%) later than that. From 6 patients (1.3%) the time to treatment was unknown. A significant higher number of men presented within 2 hours after onset of pain rather than later. Other patient characteristics, as shown in table 5.4-1, showed no relevant differences.

Table 5.4-1. Baseline characteristics of 468 prehospitally treated patients, with subdivision in time to treatment.

Time to treatment (TTT)	all patients *n=468 (100%)*	TTT ≤ 2 hours *n=291 (62%)*	TTT > 2 hours *n=171 (37%)*	TTT unknown *n=6(1%)*	p
Age (mean ± SD; yrs)	62.9±11.9	61.6±12.0	65.3±11.6	61.3±9.9	n.s.
Male (%)	322 (68.8)	218 (74.9)	100 (58.5)	4 (66.7)	p<0.02
Risk factors					
• hypertension	134/459 (29.2)	81/285 (28.4)	52/168 (31.0)	1/6 (16.7)	n.s.
• prior myocardial infarction	73/467 (15.6)	41/290 (14.1)	31/171 (18.1)	1/6 (16.7)	n.s.
• current smoker	234/438 (53.4)	155/273 (56.8)	77/159 (48.4)	2/6 (33.3)	n.s.
• diabetes	41/459 (8.9)	24/288 (8.3)	17/171 (9.9)	0	n.s.
• hyperlipidaemia	240/419 (57.3)	141/255 (55.3)	96/158 (60.8)	3/6 (50.0)	n.s.
Presentation					
• heart rate (mean ± SD; beats/min)	74.8±20.1	71.2±17.1	81.6±22.3	56.7±29.2	n.s.
• systolic blood pressure (mean ± SD; mm Hg)	128±26	127±25	131±27	116±33	n.s.
• diastolic blood pressure (mean ± SD; mm Hg)	71±16	70±17	72.±16	72±22	n.s.
• Killip class II-IV	65 (13.9)	34 (11.7)	31 (18.1)	0	n.s.
Location of infarction					
• anterior	201 (43.0)	121 (41.6)	77 (45.0)	3 (50.0)	n.s.
• inferior	135 (28.8)	86 (29.6)	49 (28.7)	0	n.s.
• inferior + right ventricle	105 (22.4)	70 (24.1)	33 (19.3)	2 (33.3)	n.s.
• other	27 (5.8)	14 (4.8)	12 (7.0)	1 (16.7)	n.s.
Time to treatment					
• median (min)	97	75	177	n.a.	-
• mean ± SD (min)	128±107	72±25	223±126	n.a.	-
ECG characteristics					
• mean sum of ST-segment deviation+ SD (mV)	1.88±9.7	1.87±0.9	1.90±1.0	1.1±0.5	n.s.
• mean sum of ST-segment elevation+ SD (mV)	1.66±9.7	1.64±0.9	1.71±1.0	0.8±0.5	n.s.

Data presented are numbers of patients with available data, with percentages between brackets

Time gain

In an earlier study performed in the Nijmegen region, time intervals of ambulance arrival, prehospital assessment, transport times and hospital delays were recorded and compared in patients treated prehospitally or in-hospitally.[5] Using the median time interval between ambulance arrival and in-hospital treatment from the aforementioned study, a median time gain of 60 minutes could be calculated, compared to the in-hospital time to treatment if no prehospital treatment would have been available.

Outcome

Patients are divided according to time to treatment (table 5.4-2). The median time to treatment was 75 minutes in the patients treated early and almost 100 minutes later in the late treatment group. Stroke did not differ in both groups, with 1 patient suffering a haemorrhagic stroke in the reteplase group, and 9 patients in the anistreplase group (7 haemorrhagic stroke, 2 patients cerebral infarction).

There is a trend to a lower incidence of rescue angioplasty in the late treatment group, but this did not reach statistical significance. Overall heart failure was recorded in 16.4% of patients. Both mortality and heart failure were respectively 5.5% and 12.7% in the early treatment group, which was significantly lower compared to the late treatment group.

Table 5.4-2. Outcome according to time to treatment.

Variable	All patients *n=468 (100%)*	TTT ≤ 2 hours *n=291 (62%)*	TTT > 2 hours *n=171 (37%)*	TTT unknown *n=6 (1%)*	p
time to treatment (median, min)	97	75	177	n.a.	
stroke	10/459 (2.2)	4/288 (1.4)	6/171 (3.5)	0 (0.0)	n.s.
rescue angioplasty	29/467 (6.2)	25/291 (8.6)	4/170 (2.4)	0/6 (0.0)	n.s.
heart failure in 30 days	75/458 (16.4)	36/284 (12.7)	39/168 (23.2)	0/6 (0.0)	p<0.02
30 day mortality	42/468 (9.0)	16/291 (5.5)	26/171 (15.2)	0/6 (0.0)	p<0.02

Table 5.4-3. Overall 30-day mortality and its causes.

Cardiogenic shock, VSR, tamponade, EMD	13 (30.9%)
Heart failure	8 (19.0%)
Re-infarction	3 (7.1%)
Intractable arrhythmia	3 (7.1%)
Hemorrhagic or non-hemorrhagic stroke	5 (11.9%)
Intestinal bleeding	1 (2.4%)
Other	6 (14.3%)
Total	*42 (100%)*

VSR = ventricular septum rupture
EMD = electromechanical dissociation

Overall 30-day mortality was 9.0% (table 5.4-3). Cardiogenic shock, ventricular septum rupture, tamponade and electromechanical dissociation were taken together (13 patients, 30.9%), because of similar clinical features in their presentation. Both stroke and heart failure were more common (11.9% and 19.0% respectively) compared with other causes of death.
Stepwise logistic regression analysis included time to treatment, site of infarction, Killip class, systolic blood pressure and heart frequency at presentation and age, sex, and risk factors as hypertension, prior infarction, hyperlipidaemia and diabetes. Using this analysis the following parameters showed a relation with 30-day mortality: age, actual time to treatment, hypertension and prior myocardial infarction. (table 5.4-4).

Table 5.4-4. Stepwise logistic regression analysis for prediction of 30-day mortality.

Variable	Odds ratio	Wald 95% confidence limits	Parameter estimate	P
Age (year)	1.06	1.03 - 1.09	0.06	0.0001
Time to treatment (minutes)	1.005	1.002 - 1.007	0.005	0.0001
Prior infarction (yes/no)	2.4	1.2 - 4.8	0.86	0.018
Hypertension (yes/no)	2.4	1.3 - 4.5	0.88	0.0059
Intercept	.		-7.16	

Age, hypertension and time to treatment were also identified as predicting heart failure within the first 30 days, as was hyperlipidemia. (table 5.4-5).

Table 5.4-5. Stepwise logistic regression analysis for prediction of heart failure.

Age (year)	1.05	1.02 - 1.07	0.044	0.0014
Time to treatment (minutes)	1.002	1.00 - 1.004	0.002	0.0464
Hyperlipidaemia (yes/no)	2.4	1.3 - 4.5	0.87	0.0072
Hypertension (yes/no)	1.9	1.1 - 3.4	0.64	0.0327
Intercept			-5.68	

5.5 Discussion

There is general consensus to treat patients with acute ST elevation myocardial infarction as soon as possible after onset of symptoms. It agrees with the concept of evolving myocardial infarction, and also with studies and meta-analyses linking infarct salvage and mortality with time to treatment.
However, in the literature about thrombolysis there are few reports of patients treated within one or two hours after onset of pain. This means that the gain in mortality is estimated by combining data from various trials, as has been performed by a linear regression analysis[6] and by a best-fit non-linear regression analysis.[2] Awareness of the importance of time to treatment have significantly shortened delays in patients treated in-hospital in the period from 1990-1998,[7] which may be the reason that in individual randomized trials comparing prehospital and hospital therapy mortality reduction is difficult to prove.[1] Furthermore, the time to treatment in-hospital is positively influenced, if the same hospital has a prehospital treatment program.[8] Moreover, patients with an extensive myocardial infarction seek medical help in an early phase and have a higher mortality[4], thus confounding prognosis in an early treatment group. However, a meta-analysis of 6 individual trials comparing pre- and in-hospital thrombolysis favored prehospital treatment, where prehospital thrombolysis reduced the relative risk of all-cause hospital mortality by 17%.[9]

Time to treatment

Calculating hypothetical in-hospital treatment on the basis of the recorded time intervals and the known time delays in the Nijmegen region, presented in an earlier study[5], we found a gain of time to treatment of 60 minutes. This agrees with the results of a meta-analysis of prehospital therapy.[9] In this study, as in others,[10] women with ST-elevation myocardial infarction present later than men, which has been suggested in the literature as the result of less typical symptoms.[10]

Early and late treatment

One should realize that in trials comparing prehospital and hospital thrombolysis the patients groups are confounded with patients treated late in the prehospital group and patients treated early in the hospital group. Seen in that light it seems a better idea to compare patients treated within 2 hours with those treated later than that. Because prehospital thrombolysis is the only way to treat early, such a comparison can only be performed using data from patients treated early, i.e. prehospitally.

Mortality

The GUSTO-I study provides the largest database of hospital treated patients treated within 2 hours, although this is confined to only 27 % of the patients in their study.[4,11] In our study 62 % of patients are treated within 2 hours. Overall 30-day mortality in our study is 9.0%, in agreement with hospital registries like the Fibrinolytic Therapy Trialists Collaborative Group[5] and of GISSI,[12] where there is no age limit for treatment, as in our study. One must realize that patients eligible for prehospital therapy are those with conclusive electrocardiographic changes, and thus with larger infarctions, with a worse prognosis than those with less outspoken ECG abnormalities. Nevertheless, we find a significant lower 30-day mortality rate of 5.5% in the early group compared to 15.2% in the late treatment group. This is comparable with the mortality of patients treated within 2 hours in the GUSTO-I study, which was 5.3%.[4] Age is one of the 4 significant independent risk factors for 30-day mortality. This concurs with the results of the GUSTO-1 study, which is based on the data of 41,021 patients treated with streptokinase and/or rt-PA,[11] and with the TIMI-risk score of ST-elevation myocardial infarction, based on data from 15,060

patients treated with lanoteplase.[13] In this risk score age over 75 years and systolic blood pressure lower than 100 mm Hg is scored as 3 points, age from 65-74, heart rate more than 100 beats per minute and Killip class II-IV scored as 2 points and a anterior myocardial infarction, a history of prior infarction, hypertension and diabetes scored as 1 point. Time to treatment later than 4 hours (24.3% of patients) is also allotted 1 point. Mortality at 30 days ranges from 0.9% with a score of 0 to 32.2% with more than 8 points. Since the number of patients treated very early is the main difference between our patient data and those of the TIMI-risk group, it is possible that time to treatment shorter than 2 hours overrules the statistical significance of several of the other variables investigated in the TIMI-risk analysis. This concurs with Boersma s findings, in which treatment within one hour shows an exponential mortality benefit.[2] Furthermore, a logistic regression analysis performed from the data from the pre-and in-hospital treated patients of the GREAT study, in which also 60% of patients are treated within 2 hours with prehospital thrombolysis, found age and time to treatment as the only variables predicting outcome.[14]

Heart failure

Heart failure was not registered in the GUSTO-trial and the TIMI-risk analysis, but is significantly lower in our early treatment group and confirms the findings of Milavetz,[15] who describes a greater degree of myocardial salvage, measured with technetium-99m sestamibi, in patients treated within 2 hours with angioplasty or thrombolysis. Our findings confirm those of Gotsman s group,[16] who describes 34.5 % less heart failure in a patient group treated within 1.5 hours after onset of symptoms. Hypertension as a predictor of heart failure after myocardial infarction is to be expected, as it is a traditional factor for heart failure. Hyperlipidaemia, although a well-known risk factor for coronary artery disease, is more difficult to explain as a risk factor for heart failure after myocardial infarction. It can be seen, however, as a marker of more advanced atherosclerotic disease.

Rescue angioplasty

Rescue angioplasty was not routinely performed in the period we started our prehospital thrombolysis program. A total of 29 patients (6.2%) were treated with angioplasty if on clinical grounds (no subsiding of both ST-segment ele-

vation and pain within 2 hours after starting treatment) thrombolysis was considered to have failed. Many authors have recently advocated rescue angioplasty on a routine base, for instance by transporting patients to angioplasty centers immediately after administration of thrombolytic therapy. In one study 35% of 165 patients needed rescue angioplasty because of angiographic confirmed failed thrombolysis.[17] Another study compared primary angioplasty with prehospital thrombolysis followed by routine angiographic assessment of reperfusion. Of 170 patients 29% were treated by rescue angioplasty; their 30-day mortality was comparable to 170 patients treated by primary angioplasty.[18] Seen in this light it is possible that a more liberal intervention strategy would have resulted in a lower mortality rate in the late treatment group.

Stroke

Eight patients suffered a haemorrhagic stroke (1.7%), 2 patients a cerebral infarction. The incidence of stroke of 1.7% may be higher than expected, but the figures are small. Anistreplase or reteplase, used in our study are both bolus thrombolytics. A meta-analysis has shown that bolus treatment with thrombolytics is associated with a risk of intracranial hemorrhage, varying between 0.6% and 1.1%, whereas in infusion therapy this risk varies between 0.4% and 0.9%.[19] In a study comparing double bolus reteplase with alteplase, intracranial hemorrhage is the same in both treatment groups, 0.91% and 0.87% respectively.[20] Our study investigated the importance of the 30-mortality reduction associated prehospital thrombolysis, and the incidence of stroke is not influenced by early treatment.

Implications

The American Heart Association and the American College of Cardiology Task Force for Thrombolytic Therapy recommend a door-to-needle time of 30 minutes.[21] This seems not realizable in a routine hospital practice so that prehospital treatment of myocardial infarction is the only way of treating early. We find a statistically significant lower mortality and heart failure rate in the early treatment group, which is comprised of 60% of the whole group, with a time to treatment not realizable by hospital treatment. The authors of the GREAT study estimated 21 deaths per 1000 patients treated extra by delaying treatment by 1 hour, underlining their argument that the treatment of acute myocardial infarction should take on the urgency of a cardiac arrest.[14] Both our data and the

review of the literature implicate the institution of a prehospital thrombolysis program.

5.6 Conclusion

Prehospital thrombolysis results in about two thirds of patients being treated within 2 hours after onset of symptoms in this study. Stepwise logistic regression analysis of multiple variables selected elderly patients, those with hypertension or prior myocardial infarction and time to treatment as predictors for 30-day mortality, and age, hypertension, hyperlipidemia and time to treatment as predictors for heart failure. The findings underline the importance of implementing a prehospital thrombolysis program.

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CHAPTER 6

EFFECT OF PREHOSPITAL THROMBOLYSIS ON ABORTING MYOCARDIAL INFARCTION

Comparison of prehospital and in-hospital treatment

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6.1 Abstract

On administering thrombolysis in a prehospital setting, we found a threefold increase in the incidence of abortion of myocardial infarction, compared with the in-hospital program of a nearby hospital. Assessment of aborted myocardial infarction may be a better criterion for the efficacy of early thrombolysis than mortality data.

6.2 Introduction

To shorten the delay between coronary occlusion and thrombolytic treatment, we initiated a prehospital thrombolysis program, working in close cooperation with our local general practitioners and ambulance service. We found that thrombolytic treatment could be instituted 63 minutes earlier than in hospital. Furthermore, 28% of patients in the prehospital group were treated within 1 hour of symptom onset, a speed not matched by any patient in the hospital group. After 2 hours these percentages became 65% and 25% respectively.[1] Although a lower mortality rate is expected in earlier treated patients, this has been difficult to prove statistically with randomized trials.[2] Patients with an extensive acute myocardial infarction and thus a high mortality tend to seek help earlier, are easily diagnosed because of decisive electrocardiographic changes, and are thus favorable candidates for very early - prehospital - thrombolysis. A high mortality rate is thus found in the very early treated group, part of which would never have survived long enough for in-hospital thrombolysis. Indeed, the GUSTO-trial confirms a higher mortality in very early treated patients.[3] We therefore evaluated our prehospital thrombolysis program by comparing the number of aborted myocardial infarcts against those of patients treated in a nearby hospital lacking such a prehospital program.

6.3 Patients and methods

Transtelephonic electrocardiograms from patients with chest pain and the suspicion of acute myocardial infarction by general practitioner or ambulance staff (duration of pain more than thirty minutes and less than six hours, not relieved by sublingual nitroglycerin) were transmitted to the coronary care unit of one of our hospitals. More than 0.1 mV ST-segment elevation in two anatomically contiguous leads or more than 0.2 mV in V1 and V2 confirmed the diagnosis of transmural myocardial ischaemia. A checklist was used to assess contra-indications for thrombolytic therapy, following which 30 mg of anistreplase was given intravenously, as well as 160 mg of aspirin chewed. A total of 227 patients were treated in the prehospital setting. Their data were compared retrospectively with those of 269 patients who underwent in-hospital thrombolyt-

ic therapy (1.5 million units of intravenous streptokinase or 100 mg of intravenous recombinant tissue plasminogen activator (rt-PA) and intravenous heparin) in the same period in a nearby hospital not using a prehospital thrombolysis program (Hospital Rijnstate in Arnhem). Details are given in table 6.3-1. The diagnosis of aborted myocardial infarction was made for both groups if 1) the combination of chest pain and transient electrocardiographic changes suggested transmural ischaemia and 2) if a rise in creatine kinase and its isoenzym > 2 times the normal value failed to appear, and 3) the cumulative ST-segment elevation and depression decreased to less than 50% within 2 hours of treatment. All ST-segment shifts were measured by the same observer, using handheld calipers at 80 msec after the J-point in all 12 leads.

Table 6.3-1 Patient characteristics

	Prehospital Thrombolysis N=227	In-hospital Thrombolysis N=269
Age (mean)	63	62
Men (number)	171 (75%)	192 (71%)
Minutes to Treatment	90*	155*
Transmural ischaemia on initial ECG		
• anteroseptal	100 (44%)	120 (45%)
• inferior	62 (28%)	76 (29%)
• inferior + right ventricle	47 (21%)	60 (23%)
• lateral or other	18 (8%)	13 (5%)
Inadvertently treated	3	5
Aborted Infarction	30 (13%)*	12 (4%)*
Total ST-segment shift (mean)	1.9 mV	1.5 mV
Coronary angiography	78 (34%)	98 (36%)
• no visible disease	3	5
• 1 vessel	41	50
• 2 vessel	21	23
• 3 vessel	13	20
Treatment		
• conservative	160 (71%)	207 (77%)
• angioplasty	46 (20%)	38 (14%)
• bypass surgery	21 (9%)	24 (9%)
Mortality at 12 months	24 (11%)	25 (9.2%)

* $p < 0.05$ prehospital versus in-hospital thrombolysis

6.4 Results

In the prehospital group 3 patients (1.3%) who underwent thrombolytic therapy showed no rise in cardiac enzymes, while, viewed retrospectively, the history and electrocardiograms of these patients suggested no myocardial ischaemia. In the hospital group 5 patients (1.9%) also received thrombolytic therapy without justification. Our analysis excluded all these patients (table 6.3-1).

A total of 30 of the 224 patients (13.4 %) of the prehospital group and 12 of the 266 (4.5 %) in-hospital group thus fulfilled the criteria for an aborted myocardial infarction ($p < 0.05$, chi-square-test).

Seven of the prehospital thrombolysis patients with aborted infarction were treated within 1 hour, but none of the in-hospital thrombolysis patients achieved this. About half of the patients in both groups had one vessel disease. Three of the prehospital treated patients and 2 of the hospital treated patients had no visible disease at angiography although they had shown an extensive ST-segment shift in the acute phase, suggesting acute anterior infarction, and a hypokinetic segment at ventriculography or echocardiography (table 6.4-1). None of the patients of either group died during their stay in hospital or before the follow up at 12 months.

Table 6.4-1 Aborted myocardial infarction after pre- and in-hospital thrombolysis

	Prehospital Thrombolysis n=30	In-hospital Thrombolysis n=12
Age (mean)	62	55
Men (number)	22	9
Minutes to treatment	85*	165*
Transmural ischaemia		
• anteroseptal	13 (43%)	9 (75%)
• inferior	13 (43%)	2 (17%)
• inferior + right ventricle	3 (10%)	1 (8%)
• lateral	1 (3%)	0
Total ST-segment shift (mean)	1.2 mV	0.9 mV
Coronary angiography		
• no visible disease	3	2
• 1 vessel	10	5
• 2 vessel	4	1
• 3 vessel	2	3
Treatment		
• conservative	17	3
• angioplasty	9	6
• bypass surgery	4	3
Mortality at 12 months	0	0

* $p < 0.05$ pre- versus in-hospital thrombolysis

6.5 Discussion

Prehospital initiation of thrombolytic therapy bodes well for patients with acute myocardial infarction, but is fraught with medical, legal and organizational problems. Training of ambulance personnel and general practitioners is time consuming, and many health providers wonder whether the effort is worthwhile. Our prehospital thrombolysis program has reduced time to treatment by a median of 63 minutes,[1] but has shown no mortality benefits, due to the huge patient cohort and/or lengthy period between prehospital and hospital thrombolysis needed to detect any significant reduction in mortality.[4] The GUSTO-I study with 41021 patients found an increase in mortality as time to treatment increased, although patients treated within one hour after symptom onset showed a higher mortality than those treated between one and three hours.[3] The study of Barbash which compared early and late treated patients, found more revascularisation procedures in patients in the early treated group, confirming the idea that this group contains patients with a worse prognosis.[5] Furthermore, a patient with a large ST-segment shift on the prehospital electrocardiogram, and thus with a larger infarction, is easier to diagnose in the prehospital setting than one with only minimal ST-segment changes who will thus be assessed and treated in hospital. Also, the GREAT study showed that patients with a large infarct and a worse prognosis tend to seek help earlier, thus confounding the mortality analysis of prehospital thrombolysis trials.[4] However, the meta-analysis of randomized prehospital thrombolysis trials as performed by Boersma et al revealed a highly significant mortality reduction in favor of early treatment and thus of prehospital thrombolysis.[6] Hence, comparison of patients without a randomization procedure will result in a population with larger infarcts and a higher mortality rate in the prehospital situation, and renders mortality a dubious criterion. An alternative parameter was therefore sought. In light of Reimer and Jennings model of evolving myocardial infarction,[7] we hypothesized that earlier thrombolytic treatment might result in a larger percentage of abortion of myocardial infarction.

Aborted myocardial infarctions have not previously been suggested as an indicator for the efficacy of prehospital thrombolysis, although most studies emphasize the importance of very early thrombolytic treatment. The GREAT study found less q-wave infarctions in the prehospital group, which could indi-

cate a greater number of aborted infarctions.[4] Also, in a ECG-substudy, the GREAT-authors found that the proportion of patients showing a reduction in ST elevation of >25% or even >50% between the home and hospital recordings was significantly greater in the early than in the late group. Although not mentioned, this is also suggestive of abortion of myocardial infarction.[8] In another study a highly significant salvage of myocardium in patients treated within 2 hours of onset of pain was reported using Technetium-99m sestamibi injections before thrombolysis and again at hospital discharge.[9]
By definition, patients with an aborted infarction lack an enzyme rise, just as do patients inadvertently treated with thrombolysis. Retrospective analysis of the electrocardiograms showed the same number of inadvertently treated patients in both prehospital and hospital groups. This compares well with 1% false positive electrocardiograms mentioned in the REPAIR study,[10] and the 1.1% reported in a study examining inadvertent thrombolytic therapy.[11] After correction for these data we found a significantly higher number of aborted infarctions in the prehospital group than in the group receiving treatment in hospital. This is probably due to the earlier time to treatment, since 7 of the 30 prehospital treated patients with aborted infarction had a time to treatment of less than one hour. None of the 12 hospital treated patients with aborted myocardial infarction were treated within one hour. So, although infarction can be aborted by thrombolytic treatment in a hospital setting, probably because myocardial tissue is preserved by collateral blood flow before the artery is opened (stuttering infarction), an infarction can also be aborted by giving very early treatment, which in our experience is only possible via prehospital thrombolysis.

6.6 Conclusion

Very early - prehospital - thrombolysis is associated with a 3-fold increase in abortion of myocardial infarction when compared with in-hospital treatment. Assessment of the number of aborted myocardial infarctions may well be a better criterion than mortality for the efficacy of early thrombolysis, in especially when small patient cohorts are studied.

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CHAPTER 7

ABORTION OF ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AFTER REPERFUSION THERAPY

Incidence, patients characteristics and prognosis

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7.1 Abstract

Objectives: We studied the incidence of reversal or abortion of myocardial infarction with prehospital thrombolysis compared with in-hospital treatment. Furthermore, the time-span was investigated, in which abortion of myocardial infarction can be expected, and the characteristics of patients with aborted versus established myocardial infarction.

Methods: From patients suspected of acute myocardial infarctions, ECG s were transmitted by the ambulance service to the coronary care units of one of our two hospitals here in Nijmegen. Myocardial infarction was confirmed in 475 patients, who were treated with prehospital thrombolysis. Their data were retrospectively compared with those of 269 in-hospital thrombolised patients at another (Arnhem) hospital that does not use a prehospital thrombolysis program. Aborted myocardial infarction is defined as the combination of subsiding of the cumulative ST-segment elevation and depression to less than 50% of the level at presentation, together with a rise of creatine phosphokinase of less than 2 times the upper normal value. A stepwise regression analysis was used to test independent predictors for aborted myocardial infarction.

Results: After correction for unjustified thrombolysis, 80 patients (17.1%) of the 468 prehospital treated patients and 12 (4.5%) of the 264 in-hospital treated patients fulfilled the criteria of aborted myocardial infarction. There was no difference in age, sex, risk factors, hemodynamic status at presentation, and location of infarction of aborted myocardial infarction compared to established ST elevation myocardial infarction. More than 30% of these patients who underwent angiography had 2- or 3-vessel disease. Apart from time to treatment, which was significantly shorter in the patients with aborted myocardial infarction (86 versus 123 minutes, p=0.05), a lower ST elevation and a higher incidence of preinfarction angina were independent predictors for abortion of myocardial infarction. The prognosis of patients with aborted myocardial infarction is significantly better compared with established myocardial infarction: 12 month mortality of 2.2% and 11.6%, respectively.

Conclusion: Prehospital thrombolysis is associated with a fourfold increase of

abortion of myocardial infarction when compared to in-hospital treatment. A shorter time to treatment, a lower amount of ST elevation and a higher incidence of preinfarction angina were predictors of abortion of myocardial infarction.

7.2 Introduction

In an earlier study using a prehospital strategy, we found that thrombolytic treatment could be instituted on average 60 minutes earlier than in-hospital thrombolysis.[1] Considering the Reimer and Jennings experiments, where the amount of myocardial damage brought about by temporary closure of a coronary artery is found to be time dependent,[2] the possibility of *reversal* or *aborted* myocardial infarction being a factor in our results suggested itself.
We found an almost threefold higher incidence of aborted myocardial infarction in the prehospital group.[1] The database of prehospital treated patients has been extended. In this report the time-span between symptom onset and treatment during which abortion of myocardial infarction can be expected is studied, as well as the patients parameters of aborted myocardial infarction compared with established ST-segment elevation myocardial infarction.

7.3 Patients and methods

Transtelephonic ECG s from patients with chest pain and suspected acute myocardial infarction (duration of chest pain more than thirty minutes and less than six hours duration, not relieved by sublingual nitroglycerin) were transmitted to the coronary care unit of one of two Nijmegen hospitals. Transmissions were performed by the ambulance staff. More than 0.1 mV ST-segment elevation in two anatomically contiguous leads or more than 0.2 mV in V1 and V2 confirmed the diagnosis of transmural myocardial ischaemia. A checklist was used to assess the contra-indications for thrombolytic therapy, and 30 mg of intravenous anistreplase or 10 U of reteplase double bolus i.v. was given, as well as 160 mg of aspirin chewed. A total of 475 patients were treated from 1995 to 2000, in the prehospital setting: 407 (86%) with anistreplase and 68 (14%) with reteplase. Their data were compared retrospectively with those of 269 patients, treated between 1995 and 1997, who underwent in-hospital thrombolytic therapy with either 1.5 million units of intravenous streptokinase (212 patients, 79%), or 100 mg of frontloaded intravenous recombinant tissue plasminogen activator (57 patients, 21%) and intravenous heparin. The latter patients were all treated in an Arnhem hospital not then using a pre-

hospital thrombolysis program.
For the purpose of this analysis, the names of treated patients were collected by ambulance staff in Nijmegen (using the prehospital strategy), or by the hospital pharmacist of the Arnhem hospital (using in-hospital thrombolysis). In this way all patients treated with fibrinolysis were included in the survey, regardless of the diagnosis at hospital discharge.
Apart from the ambulance recorded ECG s of the prehospital group, ECG s were made at submission in hospital, 2 hours after time to treatment, the following day, a week after submission and at hospital discharge. All ST-segment shifts in the ECG s of both groups were measured by the same observer, using handheld calipers at 80 msec after the J-point in all 12 leads. This observer was not informed about the cardiac enzyme concentration of the patients.
Blood samples for the determination of cardiac enzymes (creatine kinase or creatine kinase-MB-fraction and aspartate aminotransferase) were collected, at hospital admission and at 8-hour intervals, until 2 successive drops in the level of creatine kinase.
A diagnosis of aborted myocardial infarction was reached as follows: 1) when the combination of chest pain and transient ECG changes suggested transmural ischaemia, and 2) a rise in creatine kinase or creatine kinase-MB-fraction more than double the normal value failed to appear, and 3) the cumulative ST-segment elevation and depression decreased to less than 50% of the value at presentation within 2 hours of treatment. Two groups are analyzed, patients diagnosed with aborted myocardial infarction, and those with established myocardial infarction. Fibrinolysis was considered to be unjustified when 1) creatine phosphokinase levels remained less than twice the upper level of normal, and 2) the ST elevation on the ECG at presentation did not change during 48 hours following thrombolytic therapy.
Stepwise logistic regression analysis was used to test the incidence of aborted myocardial infarction against time to treatment, prior myocardial infarction, prior angina pectoris, hypertension, smoking habit at presentation, diabetes, anterior myocardial infarction, Killip class greater than 1, TIMI-risk score, systolic blood pressure and heart rate at presentation. Prior angina pectoris was present if patients had been complaining of characteristic chest discomfort within 2 weeks before presentation. Because of large standard deviations in both the aborted infarction group and the established infarction group, the

parameter time to treatment was used dichotomized in time to_treatment ≤ 2 hours and > 2 hours.

Statistical analysis was performed using standard methods, the baseline characteristics of the two groups being compared by means of the Student t test, and the frequencies in each group by means of chi-square analysis. The time intervals of patients treated prehospitally or inhospitally and of aborted and established groups were compared using the Wilcoxon rank test. Univariate contingency tables were analyzed with the uncorrected chi-square test. The level of significance used was 5%.

7.4 Results

Patient characteristics

Table 7.4-1 shows the basic characteristics of the prehospital and in-hospital treated patients. There were no clinical significant differences between the prehospital and the in-hospital fibrinolytic treatment groups, except the time to treatment, which was nearly 1 hour shorter in the prehospital group.

Table 7.4-1. Characteristics of all patients.

	Prehospital thrombolysis n = 475	In-hospital thrombolysis n = 269	p
Age (mean) (years)	63	62	n.s.
Men, n (%)	329 (69)	192 (71)	n.s.
Minutes to treatment (median, minutes)	98	155	p< 0.05
Transmural ischaemia on initial ECG,* (n, %)			
• anteroseptal	207 (44)	120 (45)	n.s.
• inferior	135 (28)	76 (29)	n.s.
• inferior + right ventricle	105 (22)	60 (23)	n.s.
• lateral	19 (4)	7 (3)	n.s.
• other	9 (2)	3 (1)	n.s.
• unknown	0	3 (1)	n.s.
Unjustified fibrinolysis	7 (1.5)	5 (1.9)	n.s.

* unjustified thrombolysis included

Unjustified fibrinolysis

Of the 475 prehospital patients, 7 (1.5%) of those treated with thrombolytic therapy showed no rise in cardiac enzymes, while retrospectively, the history and ECG s of these patients suggested no myocardial ischaemia. Two of these patients had gastritis, 1 patient esophagitis. One patient was diagnosed as having pericarditis, 2 patients showed early repolarisation on the presenting ECG, and 1 patient had left bundle branch block, which was in fact an exclusion criterion for prehospital thrombolysis. In the in-hospital group, 5 patients (1.9%) were unjustifiably treated with fibrinolysis, 4 had coronary artery disease, and one showed pericarditis. None of these patients had complications from the fibrinolytic therapy; all were excluded from this analysis.

Table 7.4-2 again shows the characteristics of prehospital and in-hospital treated patients, excluding those who received unjustified treatment.

Table 7.4-2. Characteristics of prehospital and in-hospital treated patients, with unjustified fibrinolysis excluded.

	Prehospital thrombolysis n = 468	In-hospital thrombolysis n = 264	P
Age (yrs)	63	62	n.s.
Men (%)	322 (68.8)	190 (72.0)	n.s.
• Time to treatment (median)	97	153	<0.05
• Time to treatment (mean)	128	183	n.s.
• Maximal time to treatment	305	353	n.s.
Risk factors n(%)			
• Hypertension	134/459 (29.2)	64/261 (24.2)	n.s.
• Prior MI	73/467 (15.6)	29/264 (11.0)	n.s.
• Prior angina	174/451 (38.6)	105/262 (40.1)	n.s.
• Current smoker	234/438 (53.4)	136/261 (52.1)	n.s.
• Diabetes	41/459 (8.9)	29/261 (11.1)	n.s.
Presentation			
• Heart rate (beats/min)	74.8	75.7	n.s.
• Systolic blood pressure	128	132	n.s.
• TIMI-risk score	2.8	2.5	0.05
• Killip class II-IV, n(%)	65 (14)	15 (6)	<0.01
Location of infarction, n (%)			
• Anterior	201 (42.9)	117 (44.3)	n.s.
• Inferior	135 (28.8)	78 (29.5)	n.s.
• Inferior + right ventricle	105 (22.4)	60 (22.7)	n.s.
• Other	27 (5.8)	9 (3.4)	n.s.
ECG-characteristics			
• Sum of ST segment elevation (mV, mean)	1.7	1.5	n.s.
Aborted myocardial Infarction, n (%)	80 (17)	12 (4.5)	P<0.05

Data presented are numbers of patients data are known of and percentages between brackets. MI = myocardial infarction

A total of 92 patients fulfilled the criteria of abortion of myocardial infarction, 12 (4.5%) in the in-hospital treated patients and 80 (17.1%) in the prehospital group. In the case of patients who died within 24 hours, a peak creatine kinase cannot be measured. In this way they can defy inclusion among the group diagnosed as aborted myocardial infarction cases. In our database, we found 12 patients who died within 24 hours, each of them showing a normal creatine kinase at presentation, but in whom peak creatine kinase could not be assessed. Among these patients, 7 presented with cardiogenic shock. No patient experienced a decrease of pain or ST-segment elevation within 2 hours after presentation, so that although no creatine kinase-peak was known, none of these patients fulfilled the criteria for diagnosis as aborted myocardial infarction. Three of the in-hospital treated patients died within 24 hours; all had CK-MB concentrations 2 times higher than the upper level of normal. There was a significantly higher number of patients with Killip class II, III or IV at presentation in the prehospital group, together with a higher mean TIMI-risk score. Five of the prehospital thrombolysis patients presented with Killip IV, of whom 4 died within 30 days. In the in-hospital group 2 patients had Killip IV at presentation; both survived.

Time to treatment and abortion of myocardial infarction

Eight of the 264 in-hospital thrombolysis patients (3%) and 98 of the 468 prehospital thrombolysis patients (20.9%) were treated within one hour of symptom onset. A total of 80 of the 468 patients (17.1%) belonging to the prehospital group, and 12 of the 264 (4.5%) of the in-hospital group, fulfilled the criteria of an aborted myocardial infarction ($p < 0.05$).

Coronary angiography

Coronary angiography was performed, at the discretion of the attending cardiologist, in 44.2% of the prehospital and 41.3 % of the in-hospital treated patients (Table 7.4-3). In both groups, less than half of the patients had one vessel disease. Seven prehospital treated patients, and 5 in-hospital treated patients revealed no significant disease at angiography, although they had shown extensive dynamic ST-segment shifts in the acute phase, and a hypokinetic segment in the 4 cases in which ventriculography was performed.

Table 7.4-3. Characteristics of prehospital and in-hospital treated patients, with unjustified fibrinolysis excluded.

	Prehospital thrombolysis n = 468	In-hospital thrombolysis n = 264	P
Coronary angiography performed n (%)	207 (44.2)	109 (41.3)	n.s.
• No significant disease	7 (3.4)	5 (4.6)	n.s.
• 1-vessel disease	87 (42.0)	52 (47.7)	n.s.
• 2-vessel disease	49 (23.7)	23 (22.9)	n.s.
• 3-vessel disease	41 (19.8)	19 (17.4)	n.s.
• mainstem stenosis	7 (3.4)	1 (0.9)	n.s.
• not available	16 (7.7)	9 (8.3)	n.s.
Treatment 12 months, n (%)			
• no intervention	352 (75.2)	202 (76.5)	n.s.
• PCI (incl rescue PCI)	73 (15.6)	38 (14.4)	n.s.
• Bypass surgery	43 (9.2)	24 (9.1)	n.s.
Mortality at 30 days, n (%)	42 (8.9)	18 (6.8)	n.s.
Mortality at 12 months, n (%)	51 (10.9)	25 (9.5)	n.s.

Abbreviations: PCI = percutaneous coronary intervention
n.s. = no significance

Treatment at follow up

There were no differences in treatment at 12 months follow up, nor differences in mortality between the prehospital and in-hospital treatment groups (table 7.4-3).

Patients characteristics of aborted myocardial infarction

Table 7.4-4 compares patients diagnosed with aborted myocardial infarction (whether from the pre- or in-hospital groups) with those diagnosed with established myocardial infarction (again, from whichever group). The median time to treatment of aborted myocardial infarction was 86 minutes, which was significantly shorter than the 123 minutes of established myocardial infarction. Aborted myocardial infarction was not confined to early treated patients; 41.3% of patients diagnosed with aborted myocardial infarction were treated later than 2 hours.

Aborted myocardial patients show no differences in risk factors, characteristics at presentation, infarct location, or findings at coronary angiography (Table 7.4-4), compared with established myocardial infarction, although there is a tendency toward an increased incidence of one vessel disease.

Table 7.4-4. Characteristics of all patients diagnosed with aborted myocardial infarction compared with established myocardial infarction

	Aborted myocardial infarction prehospital + in-hospital n = 92 (12.3%)	Established myocardial infarction prehospital + in-hospital n = 640 (87.4%)	P
Age (yrs)	62.0	62.7	n.s.
Men (%)	63 (68.5)	449 (70.2)	n.s.
• Time to treatment (median)	86	123	0.05
• Time to treatment (mean)	123	149	n.s.
• Maximal time to treatment	305	353	n.s.
Risk factor,s n(%)			
• Hypertension	28/92 (31.1)	170/628 (27.0)	n.s.
• Prior MI	12/92 (13.0)	90/639 (14.1)	n.s.
• Prior angina	44/88 (50.0)	235/625 (37.6)	<0.05
• Current smoker	43/87 (49.4)	327/612 (53.4)	n.s.
• Diabetes	9/92 (10.0)	61/638 (9.6)	n.s.
Presentation			
• Heart rate (beats/min)	75.3	74.9	n.s.
• Systolic blood pressure	131	129	n.s.
• TIMI-risk score	2.7	2.8	n.s
• Killip class II-IV, n (%)	7 (7.6)	73 (11.4)	n.s.
Location of infarction, n (%)			
• Anterior	46 (50.0)	274 (42.8)	n.s.
• Inferior	33 (35.9)	178 (27.8)	n.s.
• Inferior + right ventricle	9 (10.0)	156 (24.4)	n.s.
• Other	4 (4.4)	32 (5.0)	n.s.
ECG-characteristics			
• Sum of ST segment elevation (mV, mean)	1.2	1.8	<0.05
Coronary angiography performed n (%)	58/92 (63.0)	258/640 (40.3)	n.s.
• No significant disease	5 (8.6)	7 (2.7)	n.s.
• 1 vessel	30 (51.7)	109 (42.2)	n.s.
• 2 vessel	12 (20.7)	60 (23.3)	n.s.
• 3 vessel	10 (17.2)	50 (19.4)	n.s.
• mainstem	0 (0)	8 (3.1)	n.s.
• not available	1 (1.7)	24 (9.3)	n.s.
Mortality at 30 days	1/92 (1.0)	59/640 (9.2)	<0.01
Mortality at 12 months, n (%)	2/92 (2.2)	74/640 (11.6)	<0.01

Data presented are numbers of patients data are known of and percentages between brackets. MI=myocardial infarction.

A stepwise logistic regression analysis showed time to treatment < 2 hours, a history of angina pectoris, and a lower level of cumulative ST-segment elevation at presentation as independent predictors for abortion of myocardial infarction (table 7.4-5). Compared with established myocardial infarction, their mortality at 12 months is significantly lower.

Table 7.4-5. Stepwise logistic regression analysis for prediction of abortion of myocardial infarction.

Variable	Parameter estimate	Standard error	Wald chi square	p
Time to treatment ≤ 2 hr	-0.6932	0.2452	7.9905	0.005
ST elevation	-0.0668	0.0165	16.3159	<0.0001
Angina pectoris	0.05543	0.2415	5.2709	0.0217
Intercept	-0.9201	0.2842	10.4843	0.0012

7.5 Discussion

In this controlled analysis we found a fourfold increase of abortion of myocardial infarction, associated with prehospital thrombolysis, in a large patient group. This result could be explained by a nearly one-hour time gain in time to treatment.

Our prehospital thrombolysis program reduces the time to treatment by a median of 56 minutes. However, it reveals no mortality benefits. This seems to contradict Boersma s meta-analysis of 22 thrombolysis trials, which shows a highly significant mortality reduction in favor of early treatment and, thus, in favor of prehospital thrombolysis.[3] However, only 11% of patients in this meta-analysis were randomized within 2 hours, while the percentage of patients actually treated within 2 hours will consequently be lower. With our prehospital thrombolysis program 66% of patients were treated within 2 hours. It thus is possible that with prehospital hospital thrombolysis a selection is made of early presenting patients with a worse prognosis. For instance, the GUSTO-I study with 41,021 patients, found a rise in mortality as time to treatment increased, although patients treated within one hour of symptom onset yielded a higher mortality than those treated between one and three hours.[4] The GREAT

study also showed that patients with a large infarct and a worse prognosis tend to seek help earlier, thus confounding the mortality analysis of prehospital thrombolysis trials.[5] As a result, comparisons made without using a randomization procedure are bound to result in populations containing larger infarcts, and thus higher mortality rates, for pre-hospital treated groups, which shows that mortality is a doubtful indicator by which to judge. Furthermore, a larger number of patients than in our study is needed to find a significant reduction in mortality.

Abortion of myocardial infarction has not previously been suggested as an indicator of the efficacy of prehospital thrombolysis. A highly significant salvage of myocardium in patients treated within two hours after onset of pain was reported using Technetium-99m sestamibi injections before thrombolysis, and again at hospital discharge, to assess the myocardium at risk.[6] The GREAT study found fewer Q-wave infarctions in the prehospital group, which might indicate a greater number of aborted infarctions, although this was not specified.[5] In a sub-study, the GREAT-authors also found that the proportion of patients showing electrocardiographic reduction of ischemia up to 50%, as compared between home and hospital recordings, was significantly greater in the early rather than in the late group. Although not mentioned in this study, this is suggestive of abortion of myocardial infarction.[7] The same was found in 13,100 patients treated with either tenecteplase or alteplase and analyzed according to resolution of ST-segment on the ECG at presentation.[8] This same study observed a significantly lower peak creatine kinase MB level in patients with complete ST resolution, compared with patients with partial or no resolution. Furthermore, the extent of ST resolution became significantly less with increasing time to treatment.

By definition, patients with an aborted infarction exhibit dynamic ECG changes, while lacking an enzyme rise, just as do patients who are unjustifiably treated with thrombolysis. Retrospective analysis of ECG s found the same number of unjustified treated patients in our pre-hospital and hospital groups. This compares well with 1% false positive ECG s mentioned in the REPAIR study,[9] and the 1% reported in another study examining inadvertent fibrinolytic therapy.[10]

No visible disease at coronary angiography can be seen in up to 5% of patients.

However, most patients with aborted myocardial infarction do have coronary artery disease, and do not differ from patients with established infarction. It may be that infarction can also be aborted by late thrombolytic treatment, the probable cause being myocardial tissue preserved by collateral blood flow before the artery is opened, or by intermittent occlusion (stuttering infarction). This phenomenon of intermittent coronary occlusion in acute myocardial infarction has been observed at coronary angiography combined with ST-segment monitoring, up to 5 hours after onset of pain, but was most distinctive in patients presenting within 3 hours. It is accompanied by improvement of ST-segment elevation. In the latter cases, the coronary artery showing intermittent occlusion could be kept open with nitrates and intracoronary streptokinase.[11] This reflects the importance of early therapy for inducing abortion of acute myocardial infarction even further.
Apart from time to treatment, a lower amount of ST elevation and a higher incidence of preinfarct angina are independent predictors of aborted myocardial infarction. One must realise that the amount of ST elevation is not a sensitive predictor of the area at risk. Nevertheless, it is likely that timely opening of an occluded coronary artery will result in preservation of myocardial tissue only if the area at risk is not too extensive.
Preinfarction angina has been associated with early coronary thrombolysis in patients with acute ST elevation myocardial infarction.[12] Furthermore, a prospective study showed significantly less 30-day events in patients with onset of angina 24 hours before a ST elevation myocardial infarction.[13] This has been explained by the phenomenon of preconditioning;[14] this may be the explanation that in our database preinfarct angina is an independent predictor for aborted myocardial infarction.

Limitations
This study was not randomized and not performed prospectively. In the thrombolytic situation, time to treatment is all-important, so that design of studies in which patients are assigned to either pre-hospital or in-hospital treatment becomes ethically unjustifiable. The Arnhem situation is comparable to that of Nijmegen in terms of population, degree of urbanization, transport times for ambulances and CCU-facilities, the key difference being that no pre-hospital treatment was available in Arnhem during the period of the study. This, togeth-

er with the fact that both patient groups reveal baseline characteristics in reasonable agreement with those occurring in the literature, we expect them to be comparable.
Both the pre-hospital and in-hospital treatment groups contain patients treated with streptokinase, rt-PA, or reteplase, in various percentages. Nevertheless, it seems unlikely that the difference in aborted myocardial infarctions is caused by different thrombolytic regimens. This is because the number of patients treated with rt-PA is higher in the in-hospital group, whereas the incidence of aborted myocardial infarction is lower for this group than it is for the prehospital group.

7.6 Conclusion

Prehospital thrombolysis in acute myocardial infarction results in a one hour gain in time to treatment and in a fourfold increase in abortion of myocardial infarction, over that found with in-hospital treatment. A shorter time to treatment, a lower amount of ST elevation and a higher incidence of preinfarction angina were predictors of abortion of myocardial infarction. Assessment of the number of aborted myocardial infarctions may well be a better indicator for the efficacy of early thrombolysis than the currently used mortality rates, especially when small patient cohorts are studied.

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Chapter 8

Primary angioplasty or prehospital thrombolysis resulting in abortion of myocardial infarction

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8.1 Abstract

Objectives: Earlier studies showed a three times higher rate of aborted myocardial infarction in patients treated by prehospital thrombolysis, compared to in-hospital thrombolytic treatment. Combining prehospital infarct triage with angioplasty has reduced symptom-to-balloon times considerably. Reperfusion times with primary angioplasty and prehospital triage were compared with prehospital thrombolysis. The incidence of aborted myocardial infarction was assessed in groups of patients treated with either strategy.

Methods: Abortion of acute ST elevation myocardial infarction is defined by resolution of characteristic symptoms and ECG-changes, combined with a less than 2 times rise of cardiac enzymes. A total of 545 patients were treated prehospitally in the cities Rotterdam and Nijmegen and compared with 236 patients treated with primary angioplasty after prehospital triage in Zwolle. All patients were treated with aspirin prehospitally. Prehospital thrombolysis consisted of streptokinase or anistreplase in Nijmegen or Rotterdam and 10.000 IU heparin intravenously in Zwolle before transport. Time to reperfusion is defined as symptom to balloon time in primary angioplasty or symptom to thrombolysis plus 60 minutes in prehospital thrombolysis.

Results: Aborted myocardial infarction is seen in 16% of the prehospital thrombolysis patients and 11% in the primary angioplasty with prehospital triage group. In primary angioplasty, reperfusion time categorised as earlier and later than 2 hours, showed a significantly higher incidence of aborted myocardial infarction in the early treatment group. A shorter time to treatment and lower ST elevation were independent variables for aborted myocardial infarction.

Conclusion: Both prehospital thrombolysis and primary angioplasty with prehospital triage is associated with abortion of myocardial infarction, showing comparable reperfusion times. In the case of primary angioplasty a significantly higher incidence of aborted myocardial infarction is seen in patients treated within 2 hours after symptom onset.

8.2 Introduction

Reperfusion therapy in acute ST elevation myocardial infarction is aimed at restoration of coronary flow. To abort an ongoing acute ST-elevation myocardial infarction may be regarded as the ultimate goal of treatment. The characteristics of aborted myocardial infarction are early improvement of ECG-changes combined with a less than 2 times rise of the cardiac enzymes creatine kinase or creatine kinase-MB. Earlier we reported a three times higher rate of aborted myocardial infarction in a group of patients treated by prehospital thrombolysis compared to another group treated in-hospitally.[1] Aborted myocardial infarction has an excellent prognosis and is probably associated with early treatment. This concurs with the results of the meta-analysis of thrombolytic trials, which favours the golden first hour of treatment.[2]
Although there are many reports of the benefit of primary angioplasty compared to thrombolytic treatment,[3-5] abortion of myocardial infarction has rarely been mentioned in the literature of primary angioplasty. One of the reasons could be the longer time to treatment of primary angioplasty compared to prehospital thrombolysis. Combining prehospital infarct triage with angioplasty has reduced door to balloon times considerably and could make time to treatment comparable to in-hospital thrombolysis.
The incidence of aborted myocardial infarction in a group of patients treated early with primary angioplasty may affirm the concept of abortion of myocardial infarction.
In prehospital thrombolysis, a shorter time to treatment, lower ST elevation and a history of pre-infarct angina are independent variables for the incidence of aborted myocardial infarction.[6] In this paper we report the reperfusion times using a prehospital thrombolysis strategy and a strategy using primary angioplasty with prehospital triage. Furthermore, the incidence of aborted myocardial infarction in the two populations of patients is assessed and correlated with the (estimated) reperfusion time in the two populations.

8.3 Patients and methods

Prehospital thrombolysis group
Data were reviewed of 562 patients diagnosed with acute ST-segment elevation myocardial infarction and treated prehospitally from 1994 until 2000 in the cities of Nijmegen and Rotterdam, The Netherlands. In Nijmegen, a cardiologist-assisted diagnosis of transtelephonic transmission of ECG s from the ambulance to the CCU was used. In Rotterdam, a computer-assisted method in the ambulance was applied. The ambulance crew, or a general practitioner, treated patients, after checking indications and contraindications. In Nijmegen, patients were given sublingual nitroglycerin, oral aspirin and a bolus of anistreplase intravenously. In Rotterdam, patients were treated with sublingual nitroglycerin, oral aspirin and intravenous streptokinase. From 1999 onwards both cities used double bolus reteplase instead of anistreplase or streptokinase. For this analysis data derived from patients between 20 and 81 years at presentation were used (n=545).

Primary angioplasty group
From November 1998 until December 2000 in the city of Zwolle 284 patients between 20 and 81 years with chest pain underwent prehospital triage by the ambulance crew, using a computer-assisted method. Where the computer criteria for ST-elevation myocardial infarction were met (see below), patients were treated with 900 mg of aspirin and 10,000 IU of heparin intravenously, and transported to hospital for immediate angioplasty. For this analysis, patients with out-of-hospital cardiac arrest and ischaemic times longer than 13 hours (n=21) were excluded, leaving 263 patients for use.

ECG-criteria of both populations
For prehospital thrombolysis an ST-segment rise of at least 0.1 mV in at least two consecutive leads of leads II, III and aVF was necessary, or more than 0.2 mV ST elevation in more than 2 precordial leads. For primary angioplasty the same prehospital criteria were stipulated, with ST elevation in I, II, III and aVF plus ST depression V1-V6 exceeding 0.5 mV.

TIMI-risk score
To describe the risk profile of the two populations, a modified TIMI-risk score[7] was used (weight was excluded because of lack of data). Since cardiogenic shock is not assessed in this risk score, Killip class 3 and 4 were noted separately. Parameters are scored and weighed in such a way that age over 75 years and systolic blood pressure lower than 100 mm Hg are scored as 3 points, age from 65-74, heart rate more than 100 beats a minute and Killip class II-IV scored as 2 points, and anterior infarction, a history of prior infarction, hypertension, diabetes and time to treatment later than 4 hours scored as 1 point.

Abortion of myocardial infarction
The diagnosis of aborted myocardial infarction was made if the following conditions were met: (1) the combination of chest pain and ECG changes suggested transmural ischaemia before treatment, and (2) a rise in creatine kinase or creatine kinase-MB-fraction more than two times the normal value failed to appear after treatment, and (3) the cumulative ST-segment elevation and depression decreased to less than 50% of the value at presentation within 2 hours after treatment. Unjustified thrombolysis was defined as a rise of creatine phosphokinase less than 2 times the upper level of normal, and no change in the ST-segment elevation on the ECG at presentation during 48 hours following thrombolytic therapy. Unjustified diagnosis of myocardial infarction for primary angioplasty was defined by normal coronary arteries, or, in the case of an open vessel at angiography, no shift in ST-segment elevation, combined with a lack of enzyme rise larger than twice the normal range.

Time to reperfusion
For the supposed reperfusion time in the prehospital thrombolysis group a 60-minute interval was added to the time to treatment of each patient. For the reperfusion time of the primary angioplasty group the time from onset of symptoms to balloon dilatation of the infarct related vessel was taken.

Statistical methods
Statistical analysis was performed by standard methods, comparing the baseline characteristics of two groups by means of the Student t test and frequen-

cies in each group by means of Chi-squared analysis. In the database of patients treated with primary angioplasty, a stepwise logistic regression analysis was used to test the incidence of aborted myocardial infarction against time to treatment, prior myocardial infarction, hypertension, smoking habit at presentation, diabetes, anterior myocardial infarction, Killip class greater than 1, TIMI-risk score, systolic blood pressure and heart rate at presentation.

8.4 Results

Prehospital thrombolysis

In the prehospital thrombolysis group 17 (3%) patients were retrospectively diagnosed as having received unjustified therapy. These patients were excluded from analysis. Table 8.4-1 shows the characteristics of patients treated with prehospital thrombolysis, excluding these patients. Table 8.4-2 shows the estimated time to reperfusion, together with the number of patients fulfilling the criteria of aborted myocardial infarction. The incidence of abortion of myocardial infarction associated with prehospital thrombolysis was 16%.

Table 8.4-1. Baseline characteristics of patients treated with prehospital thrombolysis (unjustified therapy excluded)

Characteristic	Prehospital thrombolysis (n=545)
Age (year)	61.4 ± 11.9
Men (n, %)	393 (72.1)
Anterior infarction (n, %)	223 (40.9)
Previous infarction (n, %)	79 (14.5)
Diabetes (n,%)	49 (9.0)
TIMI-risk score	2.9
Δ ST-segment (mV)	1.7
Killip class 3 & 4 at presentation (n, %)	15 (2.8)

Table 8.4-2. Reperfusion times and outcome of patients treated with prehospital thrombolysis

	Prehospital thrombolysis (n=545)
Time to reperfusion (min) median mean ± SD	 150 182 ± 99
Aborted myocardial infarction (n, %)	87 (16.0)
Haemorraghic stroke (n, %)	10 (1.8)
30 day mortality (n, %)	38 (7.0)

Primary angioplasty with prehospital triage

In the primary angioplasty group 27 patients (10.3%) did not have an acute ST-segment elevation myocardial infarction, either on arrival at hospital, or from findings at angiography, contrary to the prehospital computer analysis. These patients were excluded from the study. Table 8.4-3 shows the characteristics of the patients treated with primary angioplasty, excluding those patients just mentioned. Table 8.4-4 shows the time to reperfusion, and the number of patients fulfilling the criteria of aborted myocardial infarction. The incidence of abortion of myocardial infarction associated with primary angioplasty is 11%.

Table 8.4-3. Baseline characteristics of patients treated with primary angioplasty (unjustified therapy excluded)

Characteristic	Primary angioplasty; prehospital triage (n=236)
Age (year)	61.4 ± 11.8
Men (n, %)	169 (71.6)
Anterior infarction (n, %)	111 (47.0)
Previous infarction (n, %)	22 (9.3)
Diabetes (n, %)	27 (11.4)
TIMI-risk score	2.5
Δ ST-segment (mV)	2.0
Killip 3 & 4 at presentation (n, %)	13 (5.5)

Table 8.4-4. Reperfusion times and outcome of patients treated with primary angioplasty

	Primary angioplasty; prehospital triage (n=236)
Time to reperfusion (min) median mean ± SD	 170 209 ± 125
Aborted myocardial infarction (n, %)	26 (11.0)
Haemorraghic stroke (n, %)	0
30 day mortality (n, %)	10 (4.2)

Outcome according to reperfusion time

Table 8.4-5. Reperfusion time

	All patients	Reperfusion time ≤2 hours n (%)	Reperfusion time > 2 hours n (%)	Reperfusion time unknown n (%)	p value
Prehospital thrombolysis	545	126 (23.1)	415 (76.1)	4 (0.7)	
Primary angioplasty; prehospital triage	236	54 (22.9)	175 (74.2)	7 (3.0)	0.99

The patients were divided into two groups, showing time to reperfusion shorter or longer than 2 hours. The percentage of patients (about 23%) being reperfused within 2 hours after onset of pain was the same in both groups (table 8.4-5).

Table 8.4-6. Thrombolysis patients, divided into early and late time to reperfusion (= time to treatment + 60 minutes)

Prehospital thrombolysis	All patients n=545	Reperfusion time ≤2 hours n = 126 (23.1)	Reperfusion time > 2 hours n = 415 (76.1)	Reperfusion time unknown n = 4 (0.7)	p
Haemorrhagic Stroke (n,%)	10 (1.8)	1 (0.8)	9 (2.2)	0	0.53
Aborted MI (n,%)	87 (16.0)	26 (20.6)	60 (14.5)	1 (25.0)	0.13
30 day mortality (n,%)	38 (7.0)	5 (4.0)	33 (8.0)	0	0.18

Table 8.4-6 gives the clinical results of patients treated with prehospital thrombolysis, and table 8.4-7 those with primary angioplasty, divided according to

Table 8.4-7. Primary angioplasty patients, divided into early and late reperfusion

Primary angioplasty; prehospital triage	All patients n = 236	Reperfusion ≤2 hours n = 54 (22.9)	Reperfusion > 2 hours n = 175 (74.2)	Unknown n = 7 (3.0)	p
Haemorrhagic stroke n	0	0	0	0	1.00
Aborted MI (n,%)	26 (11.0)	13 (24.1)	12 (6.9)	1 (14.3)	0.0004
30 day mortality (n,%)	10 (4.2)	3 (5.6)	6 (3.4)	1 (14.3)	0.76

the time to reperfusion. In the prehospital thrombolysis group the median time to reperfusion of the patients having an aborted myocardial infarction was 78 minutes (mean 114 minutes, ranging from 6 to 557 minutes). In the primary angioplasty group the median time to reperfusion was 115 minutes (mean 138 minutes, ranging from 61 to 344 minutes). There was no significance in stroke, or in 30-day mortality in early and late reperfusion groups in both the thrombolysis and the primary angioplasty populations, although former showed a trend to a lower mortality in the early reperfusion group. Aborted infarction is significantly higher in the early angioplasty group.

Table 8.4-8. Characteristics of patients with abortion of myocardial infarction

	Primary angioplasty n = 236		Prehospital thrombolysis n = 545	
	Aborted Infarction n = 26	Established infarction n = 210	Aborted infarction n = 87	Established infarction n = 458
Age	61.8	61.3	60.9	61.5
Men (n,%)	20 (76.9)	149 (70.9)	59 (67.8)	334 (72.9)
Time to treatment (median)	115	178	78	95
Killip class 3 & 4 (n,%)	1 (3.8)	12 (5.7)	1 (1.1)	14 (3.1)
TIMI-risk score	2.0	2.6	2.6	2.9
Risk factors (n,%)				
• prior myocardial infarction	5 (19.2)	17 (8.1)	14 (16.1)	65 (14.2)
• diabetes	2 (7.7)	25 (11.9)	8 (9.2)	41 (9.0)
Location of infarction (n,%)				
• anterior	12 (46.2)	99 (47.1)	37 (42.5)	186 (40.6)
30-day mortality (n,%)	0	10 (4.8)	0	38 (8.3)

Tables 8.4-8 and 8.4-9 show the clinical and angiographic characteristics of aborted infarctions compared with the established infarctions in both thrombolysis and primary angioplasty populations. Apart from a lower median time to treatment in aborted myocardial infarctions in both groups, patients showed no other differences.

Table 8.4-9. Characteristics at coronary angiography

	Primary angioplasty n = 236		Prehospital thrombolysis n = 545	
	Aborted Infarction n = 26	Established infarction n = 210	Aborted infarction n = 87	Established infarction n = 458
Coronary angiography performed (n,%)	26 (100)	210 (100)	55 (63.2)	187 (40.8)
• no significant disease	0	1 (0.5)	4 (7.3)	4 (2.1)
• 1 vessel	11 (42.3)	95 (45.2)	28 (50.9)	76 (40.6)
• 2 vessel	10 (38.5)	64 (30.5)	13 (23.6)	48 (25.7)
• 3 vessel	5 (19.2)	48 (22.9)	9 (16.4)	38 (20.3)
• mainstem	0	2 (1.0)	0	7 (3.7)
• not available	-	-	1 (1.8)	14 (7.5)

Independent variables of aborted myocardial infarction and primary angioplasty

A stepwise logistic regression analysis, showed in table 8.4-10, that time to treatment and a lower ST-segment elevation on the presenting ECG are independent variables of aborted myocardial infarction.

Table 8.4-10 Regression analysis for prediction of aborted myocardial infarction in primary angioplasty.

	p	odds ratio	95% confidence intervals
Reperfusion > 2 hours	0.005	0.237	0.087 – 0.643
ST-deviation > 1.0 mV	0.011	0.282	0.106 – 0.749

8.5 Discussion

This is the first study to assess the differences in time to reperfusion in prehospital thrombolysis and primary angioplasty with prehospital triage in acute ST elevation myocardial infarction. Both prehospital thrombolysis and primary angioplasty with prehospital triage resulted in short reperfusion time, with about 23% of patients reperfused within 2 hours. This is considerably shorter than reported in the National Registry of Myocardial Infarction, with 27,080 patients treated with primary angioplasty, a median time from onset of chest pain to hospital arrival of 1.6 hours and the median time from pain onset to angioplasty of 3.9 hours.[8] Recently, a meta-analysis of 23 trials randomising hospital thrombolysis and primary angioplasty was published.[9] Time to reperfusion varied from 4.0 to 4.6 hours with primary angioplasty and time to treatment form 3.0 to 4.1 hours with thrombolysis, all much longer than our results. There is no doubt that the prehospital triage is responsible for these short treatment times.

Time to reperfusion and outcome

The advantages and disadvantages of mechanical reperfusion therapy are well known. The alternative of prehospital thrombolysis and rescue angioplasty are recommended as combining the convenience of the former with the higher reperfusion rate of the latter.[10,11] A recently published meta-analysis of clinical outcomes of 1302 patients treated with primary angioplasty and 1333 treated with in-hospital thrombolytic therapy showed a lower cardiac event rate in the primary angioplasty group.[12] The event rate of the patients treated with thrombolysis depends on the time of presentation at the hospital. However, the event rate of the patient group being treated with primary angioplasty does not seem to be time dependent. This difference is partially explained by the fact that angioplasty restores epicardial blood flow regardless of time to presentation, contrary to thrombolysis which is less effective in achieving patency after 2 to 4 hours after symptom onset.[12] In the above-mentioned meta-analysis, only patients with in-hospital thrombolysis and primary angioplasty without prehospital triage were compared. The authors correctly state in their discussion that patients actually undergoing reperfusion time in the first 1 to 2 hours after onset of symptoms are an exception, and that the number of patients treated

very early in their study is too small to allow analysis.[12]

Abortion of myocardial infarction

In the angioplasty group, patients are included on the basis of an ECG with ST-segment elevation; some are excluded because of angiographic results. In the thrombolysis group, patients are also included on the basis of the ECG, but some are excluded on clinical grounds. Obviously, this affects the structure of the groups, making them difficult to compare. Nevertheless, abortion of myocardial infarction is not confined to thrombolytic treatment; it is also associated with primary angioplasty of acute myocardial infarction. In thrombolytic therapy, abortion of myocardial infarction is not confined to the early treatment group, which can be explained by stuttering of the infarction, which has been described earlier.[13] Abortion of myocardial infarction is significantly more frequent in the patients treated with primary angioplasty within 2 hours after symptom onset, which can be explained by early and complete opening of the infarct-related vessel.

Aborted infarction is rarely mentioned in the primary angioplasty literature. One report comparing primary angioplasty with in-hospital thrombolysis in acute myocardial infarction mentioned two patients in an angioplasty group of 109 patients and one patient in a fibrinolysis group of 111 patients as having no rise in enzymes,[5] while all the other patients had an enzyme profile typical of acute myocardial infarction. This percentage is rather low, even compared with a 4% aborted infarction rate in a hospital treatment group.[1]

Apart from time to reperfusion, a lower amount of ST elevation is an independent predictor of aborted myocardial infarction in the primary angioplasty group. As has been reported earlier, in the group treated with prehospital thrombolysis time to treatment, a lower amount of ST elevation and pre-infarct angina were reported as independent variables.[6] One must realise that the amount of ST elevation is not a sensitive predictor of the area at risk. Nevertheless, it is likely that timely opening of an occluded coronary artery will result in preservation of myocardial tissue only if the area at risk is not too extensive.

Looking at the data of patients divided into early and late treatment groups it seems there are two kinds of aborted myocardial infarction: one by early and

complete reperfusion, the other by intermittent occlusion or late occlusion accompanied by collateral blood flow, which protects myocardial tissue at risk (stuttering infarction). Early, (prehospital) thrombolysis induces the former, and early angioplasty the latter.

Study limitations

This study is not a comparison between primary angioplasty and prehospital thrombolysis. Only a prospective randomised study will be able to reveal differences or agreement in the incidence of aborted myocardial infarction in these two groups. However, the findings observed in our two groups can pave the way for such a study. Time to reperfusion by thrombolysis was more or less arbitrarily chosen by adding 60 minutes to the time to treatment from symptom onset. Adding 90 instead of 60 minutes results in a reperfusion time of 160 minutes with prehospital thrombolysis. The total number of aborted myocardial infarctions will then not change of course, but their percentage in early reperfusion group will be lower.

One of the pitfalls of the diagnosis of aborted myocardial infarction is the administration of thrombolytic therapy in the absence of ST-segment elevation myocardial infarction (unjustified fibrinolysis); both have the absence of a rise in cardiac enzymes in common. Although the specificity of computer-assisted or cardiologist-assisted electrocardiographic diagnosis of ST elevation myocardial infarction is high,[14] unjustified fibrinolysis is mentioned in the literature of thrombolysis only in 1-2.5% of cases.[15,16]

Patients for primary angioplasty are referred to the intervention centre from a larger region than those for prehospital thrombolysis, so the reperfusion time for primary angioplasty can be confounded by longer transport times. Nevertheless, the symptom-to-balloon times of the Zwolle group are shorter than those mentioned in the literature, making a comparison with prehospital thrombolysis in agreement with the real world.

8.6 Conclusion

Both prehospital thrombolysis and primary angioplasty for ST-segment elevation myocardial infarction are associated with abortion of myocardial infarc-

tion in a considerable number of patients. With primary angioplasty aborted myocardial infarction was especially evident in the patient group treated within 2 hours, with time to reperfusion < 2 hours and a lower amount of ST-elevation as independent predictors. This outcome underlines the importance of early treatment with prehospital triage when choosing between primary angioplasty or prehospital thrombolysis.

8.7 References

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CHAPTER 9

PREHOSPITAL THROMBOLYSIS WITH RETEPLASE; THE NIJMEGEN/ROTTERDAM STUDY

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9.1 Abstract

Objective: The objective of this observational study was to assess time from ECG-diagnosis to treatment and time from pain onset to treatment of double bolus reteplase compared to current therapy with streptokinase or bolus anistreplase in two cities (Rotterdam and Nijmegen) in the Netherlands, where prehospital thrombolysis is an established way of treatment of acute myocardial infarction.

Methods: Prehospital thrombolysis is performed using ECG-diagnosis by the ambulance service and bolus anistreplase for treatment in Nijmegen and streptokinase infusion in Rotterdam. Reteplase or anistreplase/streptokinase was assigned open label to patients according to order of presentation on a 1 to 1 basis. All patients were treated with nitrates sublingually and aspirin orally. Time intervals were recorded by the ambulance staff.

Results: In total 250 patients were treated between April 1, 1999 and August 1, 2000. Reteplase was used in 120 patients and anistreplase/streptokinase in 130 patients. Using double bolus reteplase resulted in a significantly shorter time of treatment of a median of 81 minutes compared to a median of 104 minutes with the established therapy ($p<0.0001$). There were no differences in mortality, aborted myocardial infarction, hemorrhagic stroke and the need for rescue angioplasty in both groups.

Conclusion: In prehospital thrombolysis double bolus reteplase is associated with a shorter time to treatment than bolus anistreplase or infusion of streptokinase.

9.2 Introduction

In the development of new thrombolytic agents for acute myocardial infarction much emphasis is put on the patency of the infarct artery and the speed of reperfusion. Reteplase (rPA) is a mutant of the first generation recombinant plasminogen activator rt-PA. It has a prolonged half-life of 18 minutes, which permits administration as a double bolus 30 minutes apart. Its clinical and angiographical efficacy is comparable to front-loaded rt-PA.[1-3] Because of its bolus administration, reteplase is a favorable thrombolytic to be used in prehospital thrombolysis. Therefore, in the cities of Rotterdam and Nijmegen, where prehospital diagnosis and treatment is already an established strategy of therapy, and where time to treatment is reduced with a median of 1 hour compared to in-hospital treatment,[4] reteplase was introduced.
We performed an observational study to compare prehospital reteplase to the current prehospital treatment of bolus anistreplase in Nijmegen and intravenous streptokinase infusion in Rotterdam. The principal endpoint of the study was the further reduction of the time gain using treatment with bolus reteplase, compared with established prehospital therapy. Furthermore, the incidence of mortality, haemorrhagic stroke, rescue angioplasty, and aborted myocardial infarction was investigated.

9.3 Patients and methods

Two cities in The Netherlands, Rotterdam and Nijmegen, have extensive experience in treating acute ST-segment elevation myocardial infarction with prehospital administered thrombolysis. Nijmegen started this program in 1987, Rotterdam in 1988. Nijmegen uses transtelephonic transmission of ECG for diagnosis and intravenous bolus anistreplase for treatment. Rotterdam uses a computerized ECG for diagnosis and streptokinase infusion for treatment. Differences and similarities of their schemes are showed in table 9.3-1. Time intervals were noted by the ambulance staff on specially designed charts. Time from pain onset to treatment was deducted from the patient history and the moment the treatment was administrated by the ambulance staff.

Table 9.3-1. Differences and similarities in the Nijmegen and Rotterdam prehospital thrombolysis schemes.

	Rotterdam	Nijmegen
Diagnosis	Computer ECG	Transtelephonic transmission
Criteria ST-elevation in at least 2 subsequent leads	$\geq$ 0.6 or 0.8 mV*	$\geq$ 0.6 mV**
Conventional fibrinolysis	1.5 million U streptokinase infusion	30 mg anistreplase bolus iv

* dependent on age: > 0.6 mV in patients younger than 70 years, $\geq$ 0.8 mV in patients younger than 80 years
** no age restriction.

For this study reteplase or anistreplase in Nijmegen and reteplase or streptokinase in Rotterdam was assigned open-label and one to one in order of presentation. All patients treated in both cities received nitrates sublingually and aspirin orally. No heparin was given before prehospital treatment of either agent.

The Nijmegen patients were transported to one of the two city hospitals; the Rotterdam patients were admitted to one of eight hospitals in that region. All reteplase patients received 5000 U of bolus heparin i.v. immediately after hospital arrival, followed by heparin infusion. Names of the patients treated were given by both ambulance services, regardless of the diagnosis at discharge.

Rescue angioplasty was done at the discretion of the attending cardiologist, if there were no clinical signs of reperfusion within 2 hours after start of the treatment.

A diagnosis of aborted myocardial infarction was reached as follows: 1) when the combination of chest pain and transient ECG changes suggested transmural ischaemia, and 2) a rise in creatine kinase or creatine kinase-MB-fraction more than double the normal value failed to appear, and 3) the cumulative ST-segment elevation and depression decreased to less than 50% of the value at presentation within 2 hours of treatment.[4] Fibrinolysis was considered to be

unjustified when 1) creatine phosphokinase levels remained less than twice the upper level of normal, and 2) the ST elevation on the ECG at presentation did not change during 48 hours following thrombolytic therapy.

Statistical analysis was performed by standard methods, comparing the baseline characteristics of two groups by means of the Student t test and frequencies in each group by means of chi-square analysis. The time intervals of both groups were compared using the Wilcoxon rank test. The level of significance used was 5%.

9.4 Results

A total of 250 patients were included between April 1, 1999 and August 1, 2000. Reteplase was used in 120 patients, and 130 patients were treated with anistreplase or streptokinase. Of these 250 patients 132 were treated in Nijmegen and 118 in Rotterdam. Table 9.4-1 gives the results of the baseline characteristics of the reteplase and the anistreplase/streptokinase group. Age, sex, infarct location, risk factors and details of presentation were similar in both groups.

Table 9.4-1. Basic characteristics of both groups

	Streptokinase/ anistreplase n = 130	Reteplase n = 120	p
Age (mean, years)	61.9	62.5	0.70
Men, n (%)	86 (66)	78 (65)	0.85
Infarct site, n (%)			
• anteroseptal	45 (35)	53 (44)	0.16
• inferior	38 (29)	32 (26)	0.15
• inferior + right ventricle	41 (31)	30 (25)	0.15
• other	6 (5)	5 (4)	0.90
Risk factors, n (%)			
• hypertension	32/130 (25)	30/118 (25)	0.94
• prior myocardial infarction	15/130 (12)	20/120 (17)	0.24
• current smoker	67/125 (54)	61/119 (51)	0.63
• diabetes	13/130 (10)	12/120 (10)	1.00
Presentation			
• heart rate (beats/min)	77	75	0.49
• systolic blood pressure (mm Hg)	128	130	0.66
• diastolic blood pressure (mm Hg)	73	76	0.18
• Killip class II-IV (n,%)	16 (12)	9 (8)	0.21
Thrombolytic therapy, n			
• anistreplase	67	---	
• streptokinase	63	---	
• reteplase	---	120	

Table 9.4-2 shows that there is a significant difference in time to treatment with reteplase in comparison to therapy using anistreplase or streptokinase. The median time from arrival of ambulance to treatment was 27 minutes in the streptokinase group and 12 minutes in the reteplase group. The median time from ECG-diagnosis to administration of thrombolysis was 18 minutes in the streptokinase group and 7 minutes in the reteplase group. The total time to treatment, from pain onset to thrombolysis, was 104 minutes in the streptokinase and 81 minutes in the reteplase group. From the patients treated with streptokinase or anistreplase, 21% were treated within 1 hour; this was 27% in the patient group treated with reteplase.

Table 9.4-2. Time intervals of treatment of patients treated with streptokinase/anistreplase or reteplase (minutes)

	symptoms - arrival of GP	arrival of GP – alarm	alarm – arrival of ambulance	arrival of ambulance - ECG diagnosis	ECG diagnosis – thrombolysis	preparation for transport	transport time to hospital
	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd
streptokinase /anistreplase	55	12	10	9	18*	10	10
n = 130	75 ± 75	13 ± 13	10 ± 4	9 ± 7	18 ± 8	10 ± 7	9 ± 5
reteplase	53	8	9	5	7*	10	10
n = 120	70 ± 67	10 ± 10	8 ± 3	6 ± 6	8 ± 8	12 ± 7	10 ± 4

All times in minutes. GP=general practitioner. sd = standard deviation
* $p<0.0001$

Table 9.4-3. Time intervals of established prehospital therapy.

	symptoms - arrival of GP	arrival of GP – alarm	alarm – arrival of ambulance	arrival of ambulance - ECG diagnosis	ECG diagnosis – thrombolysis	preparation for transport	transport time to hospital
	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd	median, mean±sd
streptokinase	55	12	11	8	16	10	10
n = 63	78 ± 85	15 ± 18	10 ± 3	9 ± 9	17 ± 8	11 ± 8	9 ± 4
anistreplase	55	12	10	9	19	10	10
n = 67	73 ± 68	12 ± 7	10 ± 4	9 ± 3	19 ± 7	9 ± 7	9 ± 5

Table 9.4-3 gives the time intervals of 63 patients, treated with streptokinase infusion and 67 patients with bolus anistreplase, showing no difference between either therapies.
Table 9.4-4 shows that the incidence of aborted myocardial infarction does not differ between therapy with reteplase and conventional therapy. There is a trend towards a higher use of rescue angioplasty in the reteplase group. Also, all adverse events together, i.e. 30-day mortality, stroke and rescue angioplasty, did not reach a statistical significant difference in both groups.

Table 9.4-4. Differences in the use of anistreplase/streptokinase or reteplase in prehospital thrombolysis.

	streptokinase/ anistreplase n = 130 (%)	reteplase n = 120 (%)	p
Time to treatment (minutes) median mean ± sd	 104 122 ± 78	 81 108 ± 78	 0.04
Aborted myocardial infarction, n (%)	20 (15.4)	22 (18.3)	0.53
30-day mortality, n (%)	6 (4.6)	8 (6.7)	0.48
Stroke (haemorrhagic), n (%)	1 (0.8)	2 (1.7)	0.52
Rescue angioplasty, n (%)	11 (8.5)	17 (14.2)	0.15

Table 9.4-5 gives the final diagnosis of all patients. In 8 patients (3.2%) thrombolysis was unjustified. Most of the patients who underwent angiography had 1 vessel disease; in 3 patients (1.2%) no significant stenosis was present, 3 patients (1.2%) had main stem stenosis.

Table 9.4-5. Final diagnosis of patients in both groups

	streptokinase/ anistreplase n = 130 (%)	reteplase n = 120 (%)
Development of new Q-waves, n (%)	85 (65.4)	78 (65.0)
No development of new Q-waves, n (%)	21 (16.2)	16 (13.3)
Aborted myocardial infarction, n (%)	20 (15.4)	22 (18.3)
Unjustified fibrinolysis, n (%)	4 (3.1)	4 (3.3)
Angiography performed, n (%)	63 (48.5)	53 (44.2)
• no significant disease	2 (3.2)	1 (1.9)
• 1 vessel	23 (36.5)	25 (47.2)
• 2 vessel	24 (38.1)	12 (22.6)
• 3 vessel	12 (19.0)	14 (11.7)
• main stem stenosis	2 (3.2)	1 (1.9)

9.5 Discussion

This study shows that treatment of acute myocardial infarction with reteplase in a prehospital setting seems to be faster than the conventional therapy using anistreplase or streptokinase. The difference is apparent in the time from symptom onset to treatment, but also in the time interval between ECG-diagnosis and administration of thrombolysis. There is no difference in time to treatment using bolus anistreplase or infusion of streptokinase. Streptokinase has to be prepared in an infusion form and anistreplase has to be dissolved very careful-

ly to prevent foam formation. Both properties possibly cause delays in administration in prehospital situations. The bolus administration of reteplase does not have these disadvantages, probably an explanation of the difference in time to treatment. Most of the time intervals are shorter in the reteplase group, although these differences did not reach significance. The shorter intervals of time from alarm to the arrival of the ambulance and from their arrival to ECG diagnosis may be explained by the open nature of the study. However, the difference in time intervals before the ambulance arrived clearly can not, because the patient nor the general practitioner were informed about the nature of the thrombolytic drug that was going to be used in the event of an acute myocardial infarction. The difference of a median of 23 minutes in favor of reteplase seems to be large, but is mentioned in the literature before: using bolus reteplase rather than an intravenous rt-PA was associated with a median time gain of 17 minutes in a study of 500 in-hospital treated patients.[5] A prehospital study using reteplase[6] (TIMI-19) found a median time between arrival of the ambulance service and administration of the medication of 31 minutes and a time gain of a median of 33 minutes compared with in-hospital therapy.

Our study focused on time to treatment and is not powered to discern differences in clinical outcome. However, clinical outcome is likely to be better in early treated patients, as has been showed in meta-analyses of time to treatment[7] and of prehospital versus in-hospital thrombolysis.[8] This was also apparent in angiographic results of thrombolysis: recently published data from the TIMI 14 and InTime-II study showed that in patients treated with different reperfusion regiments (reteplase, alteplase, lanoteplase combined with abciximab) the development of TIMI 3 flow was related to time to treatment and not to the thrombolytic agent used.[9]

Aborted myocardial infarction is not confined to the use of streptokinase in prehospital thrombolysis, as has been shown before[4], but is also apparent in the reteplase group. The TIMI-19 prehospital study of reteplase found 29% of patients showing 50% resolution of their elevated ST-segments by the time these patients arrived at the emergency room, and over 70% of ST segment resolution in 15% of patients,[6] similar to the 15% and 18% of aborted myocardial infarction in our two therapy groups.

Although the 30-day mortality in our study is the same as in-hospital registries,[10-12] it is important to note that a prehospital strategy selects patients who

present early and with explicit ST-segment changes, both aspects characteristic of a large infarction.

The incidence of stroke of 1.6% (95% confidence interval 0 to 3.8%) in our reteplase group may be higher than expected, but the figures are small. A meta-analysis has shown that bolus treatment with thrombolytics is associated with a risk of intracranial hemorrhage, varying between 0.6% and 1.1%, whereas in infusion therapy this risk varies between 0.4% and 0.9%.[13] In a study comparing double bolus reteplase with alteplase, intracranial hemorrhage is the same in both treatment groups, 0.91% and 0.87% respectively.[1] Our study was observational in character, without blinded randomization, and not powered to assess a difference in mortality or stroke between conventional and reteplase therapy. The meta-analysis suggested that the incidence of stroke in bolus therapy is primarily associated with the method of administration rather than the properties of the drug. An association with the time to treatment (early or late) is not to be expected, although not studied in the meta-analysis. Bolus heparin was not administered prehospitally in this study. It was initiated as soon as the patient arrived at the hospital, and was, therefore, given before or at the same time of the second bolus reteplase. Given the half-life of 18 minutes of reteplase it seems unlikely that the administration of heparin a median of 20 minutes after the first bolus would have changed the clinical outcome. In fact, this strategy was also used in the recently published prehospital ER-TIMI 19 trial,[6] where heparin was administered as soon as possible *after* enrolment and administration of the first bolus of reteplase, either in the field or in the hospital.

There is a trend towards more clinical events in the reteplase group. This is especially apparent in the incidence of rescue angioplasty, which is about 1.5 times higher in the reteplase group. Although not statistically significant, this could be the result of the open nature of the study, in which the attending cardiologist might choose a more liberal intervention strategy when a new thrombolytic agent is used. However, compared to studies describing 29-35% rescue angioplasty after failed thrombolytic therapy,[14,15] 14.2% rescue angioplasty in our reteplase group is not unexpectedly high.

Limitations

This was not a double-blinded trial, but an observational study to assess treatment

times using prehospital strategies. The study was not powered to discriminate differences in mortality, intracranial hemorrhage or rescue angioplasty.
For the sake of simplicity heparin bolus therapy was withheld prehospitally in the reteplase group. We do not think elimination of the heparin bolus in the reteplase group is sufficient explanation for the differences in time to treatment in our study.

9.6 Conclusion and implications

Double bolus reteplase in prehospital thrombolysis is associated with a statistically significant shorter time to treatment compared with anistreplase/streptokinase. The new bolus thrombolytics, like reteplase and tenecteplase, not only provide an equivalent efficacy with regard to 30-day mortality and bleeding complications compared with established therapy[1-3,16] but also facilitate the administration of the drug. Our study shows that the reduction of time to treatment with bolus thrombolytics is considerable. This may implicate that in the case of prehospital treatment with drugs, like thrombolytic therapy, for which time is essential, bolus administration is preferable to infusion therapy.

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CHAPTER 10

PREHOSPITAL VERSUS HOSPITAL FIBRINOLYTIC THERAPY USING AUTOMATED VERSUS CARDIOLOGIST ECG DIAGNOSIS OF MYOCARDIAL INFARCTION: ABORTION OF MYOCARDIAL INFARCTION AND UNJUSTIFIED FIBRINOLYTIC THERAPY

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10.1 Abstract

Background: This study investigated the incidence of abortion of myocardial infarction and of unjustified fibrinolysis using automated versus cardiologist assisted diagnosis of acute ST elevation myocardial infarction. The results of prehospital diagnosis and treatment (2 cities in the Netherlands) were compared to those of in-hospital treatment. Unjustified fibrinolysis must be differentiated from justified thrombolysis resulting in aborted myocardial infarction. Both have the absence of a significant rise in cardiac enzymes in common. In aborted myocardial infarction this is a result of timely reperfusion, in unjustified thrombolysis the result of an incorrect diagnosis.

Methods: In the city of Rotterdam 118 patients were prehospitally treated for myocardial infarction, diagnosed using a mobile computer ECG; in the city of Nijmegen 132 patients were treated prehospitally, using transtelephonic transmission of the ECG to the CCU and judged by a cardiologist. Their data were compared with those of 269 patients treated in-hospital in the city of Arnhem, using the same ECG-criteria. Abortion of myocardial infarction was diagnosed as the absence of a significant rise in cardiac enzymes and the presence of resolution of chest pain and 50% of ST-segment deviation within 2 hours after onset of therapy. Lacking these, the diagnosis of unjustified fibrinolytic therapy was made.

Results: Unjustified treatment occurred in 8 (3.2%) prehospitally treated patients (4 in Rotterdam and 4 in Nijmegen). Of the in-hospitally treated patients in Arnhem, 5 (1.9%) were treated unjustifiably ($p=0.49$). Aborted myocardial infarction occurred in 15.3% and 18.2% in Rotterdam and Nijmegen respectively, against 4.5% in in-hospital treatment in Arnhem ($p<0.001$).

Conclusion: Abortion of myocardial infarction is associated with prehospital thrombolysis. Unjustified fibrinolysis for acute myocardial infarction occurs in prehospital fibrinolysis as frequent as in the in-hospital setting. The use of different ECG methods for diagnosing acute myocardial infarction does not seem to make any difference.

10.2 Introduction

The importance of reducing the time between onset of pain and fibrinolysis in patients with evolving myocardial infarction has been investigated extensively.[1] Using a strategy of prehospital triage and subsequent treatment, 25% of patients can be treated within one hour, a result not matched by in-hospital triage and therapy.[2] Considering the Reimer and Jennings experiments, where the amount of myocardial damage brought about by temporary closure of a coronary artery is found to be time dependant,[3] the possibility of aborted myocardial infarction suggested itself. We earlier reported that prehospital fibrinolysis is strongly associated with abortion of myocardial infarction.[2] One of the characteristics of aborted myocardial infarction is a rise in cardiac enzymes less than 2 times the upper limit of normal. However, this can also be a characteristic of inadvertent administration of thrombolytic therapy. The administration of fibrinolytic therapy to patients without acute myocardial infarction can be disastrous, as already emphasized in a few case reports from the early days of fibrinolysis.[4-7] On the other hand, failure to give fibrinolytic therapy early after the onset of pain may deprive the patient of a potentially life saving therapy. Unjustified administration of fibrinolysis can have undesirable medical and legal repercussions, especially if paramedics or nurses in the prehospital setting initiate such treatment. Two cities in the Netherlands, Rotterdam and Nijmegen, set up a prehospital thrombolysis program, working in close cooperation with local general practitioners and ambulance services, using different means of diagnosing acute infarction.

We hypothesized that prehospital thrombolysis would result in a higher incidence of aborted myocardial infarction than in-hospital treatment. Furthermore, we expected the incidence of unjustified fibrinolysis to be the same in both cities, and comparable to in-hospital fibrinolysis. To investigate this, we examined all the prehospital treated patients in both cities during one year, and compared them with patients treated in a different city (Arnhem) where no prehospital program is operational. Consequently, our study was performed to determine 1) if automated versus cardiologist-assisted ECG-diagnosis is associated with an increased incidence of unjustified fibrinolytic therapy (Rotterdam versus Nijmegen and Arnhem), and 2) whether prehospital throm-

bolysis causes an increased incidence of aborted myocardial infarction (Rotterdam and Nijmegen versus Arnhem).

10.3 Methods

Diagnosis

For use in prehospital thrombolysis in Rotterdam, a portable 12-lead computerized ECG system is used. This is adjusted in such a way that acute myocardial infarction is diagnosed if more than 0.2 mV of ST-segment elevation in ≥ 2 precordial leads (one at least 0.3 mV) is measured, or more than 0.2 mV ST-elevation in ≥ 2 extremity leads (one at least 0.2 mV). Using these criteria this computer system has a sensitivity of 60% and a specificity of 97% for detecting both anterior and inferior myocardial infarction.[8] Furthermore, this computer system can differentiate the ST-segment elevation concave to the iso-electric line of right bundle branch block, left ventricular hypertrophy and early repolarisation from the ST-segment elevation convex to the iso-electric line of acute myocardial infarction with a specificity of 98% compared to an electrocardiographer, albeit at the cost of a sensitivity of 52%.[9] The decision to treat the patient is made by the ambulance staff and is based on the result of the computer system. In Nijmegen ECG's of patients with chest pain are made by the ambulance staff and transmitted to the cardiac care unit using a transtelephonic data transmission system. There the diagnosis of acute myocardial infarction is confirmed by the attending cardiologist if more than 0.2 mV of ST-segment elevation is seen in ≥ 2 extremity leads or more than 0.3 mV in ≥ 2 precordial leads. Thrombolytic therapy was given by the ambulance staff. In-hospital fibrinolysis in Arnhem is initiated after cardiologist confirmed ECG using the Nijmegen criteria. These criteria have a sensitivity of 62% and a specificity of 98% for detecting both anterior and inferior myocardial infarction.[10] The computer ECG in Rotterdam and the ECG protocol in Nijmegen excludes patients showing left bundle branch block or signs of Wolf-Parkinson-White syndrome. Patients with electronic pacemakers are excluded from the prehospital diagnosis. In all three cities a similar checklist of contraindications for the administration of thrombolytic therapy is used, and all patients are treated with nitroglycerin and aspirin before fibrinolysis is given. Intravenous heparin is started

in all patients after hospital admission. At the time the study was conducted no eligible patients for reperfusion were treated with primary angioplasty.
For this analysis names of treated patients were collected by the ambulance staff in both cities using prehospital thrombolysis, or by the hospital pharmacist, where in-hospital fibrinolysis was given. In this way all patients treated with fibrinolysis were included in the study, regardless of the diagnosis at hospital discharge. For comparison of the 3 groups, risk factors, characteristics at presentation and the TIMI-risk score for ST elevation myocardial infarction[11] was used.

Table 10.3-1. Definitions

Aborted myocardial infarction	1. Subsiding of ST deviation $\geq$ 50% within 2 hours after fibrinolysis 2. Rise in cardiac enzymes $\leq$ 2 times upper value of normal
Unjustified fibrinolysis	1. No change in ST deviation within 48 hours after fibrinolysis 2. Rise in cardiac enzymes $\leq$ 2 times upper value of normal

Definition of aborted myocardial infarction or of unjustified fibrinolysis (Table 10.3-1)
Absence of a significant rise in cardiac enzymes will erroneously identify a so-called aborted myocardial infarction as unjustified treatment. Both aborted myocardial infarction and unjustified fibrinolysis were examined in all patients having a smaller than 2 times rise of the upper limit of cardiac enzymes (either CPK or CK-MB, and ASAT). We defined an aborted myocardial infarction if chest pain and the ST-segment deviation subsided more than 50% within 2 hours after treatment, together with a lack of a rise of more than 2 times the upper limit of normal of the above mentioned cardiac enzymes.[2] All ST-segment shifts were measured by the same observer, using handheld calipers at 80 msec after the J-point in all 12 leads. This observer was not informed about the cardiac enzyme concentration of the patients. Aborted myocardial infarction

could be ruled out if both enzymes did not rise and the ST-segment elevation of the prehospitally registered ECG did not change during a 48-hour period following administration of fibrinolysis. If, by retrospect the ST-segment deviation did not fulfill the above-mentioned criteria and there was no rise in cardiac enzymes, fibrinolysis was also designated as unjustified. Persistent ST-elevation of remote infarction, without a lack of enzyme rise, is classified as unjustified therapy, if there was no dynamic ST-segment change. All patients with unjustified fibrinolysis were classified as having *definitive* (confirmed by coronary angiography) or *probable* (chest pain and/or ECG abnormalities at an exercise test or at single photon emission tomography) coronary artery disease, or as having had nonischaemic or noncardiac chest pain.

Statistics
For statistical comparison of the number of patients having aborted myocardial infarction or unjustified fibrinolysis, use was made of the chi-square test. For difference in time intervals use was made of the Student t-test.

10.4 Results

Between April 1, 1999 and August 1, 2000 a total of 250 patients received prehospital treatment, using anistreplase, streptokinase or reteplase: 118 patients were treated in Rotterdam and 132 patients in Nijmegen. Their data were compared with 269 consecutive in-hospital diagnosed and treated patients in Arnhem during 1995-1997.

Patient characteristics
Table 10.4-1 shows the basic characteristics of the prehospital (Nijmegen and Rotterdam) and in-hospital (Arnhem) treated patients. There were no significant differences in risk factors and presentation features between the prehospital and the in-hospital fibrinolytic treatment groups. Prehospital fibrinolysis, using both means of diagnosis myocardial infarction, resulted in about 60 minutes earlier time to treatment than in-hospital therapy ($p<0.01$).

Table 10.4-1. Basic characteristics of patients treated prehospital (2 cities) and in-hospital.

	Prehospital Nijmegen n=132 (%)	Prehospital Rotterdam n=118 (%)	In-hospital Arnhem n=269 (%)	p
Age (mean,yrs)	62.8	61.5	62.1	n.s.
Men (%)	80 (60.6)	84 (71.2)	192 (71.4)	n.s.
Time to treatment (median)	105	85	155	<0.01*
Risk factors, n (%)				
• Hypertension	37/132 (28.0)	25/118 (21.2)	64/266 (24.1)	n.s.
• Prior MI	22/132 (16.7)	13/118 (11.0)	29/269 (10.8)	n.s.
• Current smoker	62/127 (48.8)	66/117 (56.4)	138/266 (51.9)	n.s.
• Diabetes	10/132 (7.6)	15/118 (12.7)	30/269 (11.2)	n.s.
Presentation				
• Heart rate (beats/min)	73	78	76	n.s.
• Systolic blood pressure	127	130	132	n.s.
• TIMI-risk score	3.0	2.6	2.6	n.s.
Location of infarction, n (%)				
• Anterior	53 (40.2)	45 (38.1)	120 (44.6)	n.s.
• Inferior	41 (31.1)	29 (24.6)	76 (28.2)	n.s.
• Inferior + right ventricle	32 (24.2)	39 (33.1)	60 (22.3)	n.s.
• Other	6 (4.5)	5 (4.2)	13 (4.8)	n.s.
ECG-characteristics				
Sum of ST segment elevation (mV, mean)	1.20	0.96	0.84	n.s.

*prehospital versus in-hospital

Table 10.4-2 presents the results of the 3 groups. Haemorrhagic stroke (neurological symptoms characteristic of intracranial bleeding, confirmed by CT-scanning of the brain) occurred in 3 patients (1.2%) treated prehospitally, and in 3 patients (1.1%) treated in-hospitally. No other severe bleeding complications occurred in the prehospital treated patients. Of the in-hospital group 2 patients had a severe bleeding complication. A total of 42 of the 250 (16.8%) prehospital treated patients and 12 of the 269 (4.5%) in-hospital treated patients fulfilled the criteria for aborted myocardial infarction ($p<0.001$). Unjustified

therapy in prehospital treatment (3.2%) was not significantly different from in-hospital therapy (1.9%).

Table 10.4-2. Clinical results of patients treated fibrinolytic therapy, prehospital (2 cities) and in-hospital.

	Prehospital Nijmegen n=132 (%)	Prehospital Rotterdam n=118 (%)	In-hospital Arnhem n=269 (%)	p
Aborted myocardial infarction (%)	24 (18.2)	18 (15.3)	12 (4.5)	< 0.001*
Unjustified fibrinolysis (%)	4 (3.0)	4 (3.4)	5 (1.9)	n.s.**
Stroke (%)	2 (1.5)	1 (0.8)	3 (1.1)	n.s.
30-day mortality	8 (6.1)	6 (5.1)	18 (6.8)	n.s.

* prehospital versus in-hospital thrombolysis.
** both prehospital thrombolysis Rotterdam versus Nijmegen as prehospital thrombolysis versus in-hospital treatment.

Remote infarction with persistent ST-segment elevation was seen in 4 patients (1 in Rotterdam and 3 in Arnhem). Although the 4 patients with persistent ST-segment elevations of remote infarction could be diagnosed as having aborted myocardial infarction, the lack of dynamic ST-segment changes lead us to classify those patients as having had unjustified therapy. Although left bundle block was excluded, in Nijmegen 2 patients with this ECG characteristic were treated prehospitally. Coronary artery disease could not be confirmed by angiography in these 2 patients. Pericarditis with persistent ST-segment elevation for more than 2 hours was seen in 1 patient (Arnhem). The time to treatment of the patients with unjustified fibrinolysis (median 89 minutes) is not different from the total prehospital treated group (median 95 minutes). Table 10.4-3 presents the discharge diagnosis and 1 year clinical follow-up treatment of the 13 patients who received unjustified fibrinolytic therapy. Statistically, there was no difference, regardless in which way the prehospital ECG-diagnosis of acute myocardial infarction was made. Ten patients had an uneventful recovery; 1 patient has acute myocardial infarction 3 days later, 1 patient was treated for heart failure and 1 had coronary bypass; all were alive at 1-year follow up.

Table 10.4-3. Admission and discharge diagnosis and follow up of patients with unjustified thrombolysis.

	admission diagnosis	time to treatment (min)	discharge diagnosis	definite CAD	1 year follow up
Rotterdam					
patient 1	ant MI	75	remote MI	+	treatment heart failure
patient 2	ant MI	92	unstable angina; 3 vessel disease	+	CABG
patient 3	ant MI	70	probable CAD, LVH on ECG	-	uncomplicated
patient 4	inf MI	100	probable CAD, ST depression	-	uncomplicated
Nijmegen					
patient 1	ant MI	200	unstable angina	+	ant MI 3 days later
patient 2	ant MI	71	atrial fibrillation with LBBB	-	uncomplicated
patient 3	ant MI	100	probable CAD; LBBB	-	uncomplicated
patient 4	ant MI	89	no CAD at angiography	-	uncomplicated
Arnhem					
patient 1	inf MI	230	remote MI	+	uncomplicated
patient 2	ant MI	150	unstable angina; 3 vessel disease	+	uncomplicated
patient 3	ant MI	n.a.	atrial fibrillation with remote ant MI	+	uncomplicated
patient 4	ant MI	140	unstable angina; remote inf MI; 2 vessel disease	+	uncomplicated
patient 5	ant MI	n.a.	pericarditis	-	uncomplicated

CAD=coronary artery disease; MI=myocardial infarction; inf=inferior; ant=anterior; LBBB=left bundle branch block; CABG=coronary bypass graft; LVH=left ventricular hypertrophy

10-5 Discussion

In this analysis we found a fourfold increase of abortion of myocardial infarction, associated with prehospital thrombolysis, compared with in-hospital treatment. Aborted myocardial infarction has not previously been suggested as an indicator for the efficacy of prehospital thrombolysis, although most studies emphasize the importance of very early thrombolytic treatment. The GREAT study found less q-wave infarctions in the prehospital group, which could indicate a greater number of aborted infarctions.[12] Also, in a ECG-substudy, the GREAT authors found that the proportion of patients showing a reduction in ST elevation of >25% or even >50% between the home and hospital recordings was significantly greater in the early than in the late group.[13] The same was found in 13,100 patients treated with either tenecteplase or alteplase and analyzed according to resolution of ST-segment on the ECG at presentation.[14] This study observed a significantly lower peak creatine kinase MB level in patients with complete ST resolution, compared with patients with partial or no resolu-

tion. Furthermore, the extent of ST resolution became significantly en less with increasing time to treatment. An electrocardiographic analysis from the TIMI 14 and the InTime-II study shows that for each additional hour from symptom onset to initiation of pharmacological reperfusion, the chance of achieving early, complete ST resolution decreases by 6%.[15] This is all suggestive of the phenomenon of abortion of myocardial infarction.

Unjustified fibrinolysis

Although prehospital thrombolysis is associated with a higher incidence of abortion of myocardial infarction compared to in-hospital treatment, this analysis shows the same incidence of unjustified fibrinolysis in two cities with a prehospital strategy and different methods of ECG-diagnosis. Ever since the initiation of intravenous fibrinolysis unpreceded by angiography, physicians have been troubled by the prospect of administering treatment in the absence of acute myocardial infarction. Case reports of unjustified fibrinolysis date from the late eighties (Table 10.5-1).

Table 10.5-1. Case reports of unjustified thrombolysis.

Author Year	number of patients	ECG criteria	diagnosis	outcome
Tilley[4] 1985	2	5	1: pericarditis 1: pericarditis	good, pericardiocentesis
Ferguson[5] 1986	1	5	pericarditis	good
Blankenship[6] 1989	2	1	1: pericarditis 1: pericarditis + aortic dissection	surgery death
Kahn[7] 1993	3	5	1: myocarditis 1: aortic dissection 1: pericarditis	good death good

Legends: ECG criteria
1=≥ 1 mm ST segment elevation in 2 contiguous leads;
2= ≥ 1 mm ST segment elevation in 2 limb leads
3= ≥ 2 mm ST segment elevation in 2 chest leads
4= ECG criteria not necessary
5= ECG criteria not mentioned
n.a.= not available

Pericarditis is the most common, and aortic dissection the most dreaded trigger leading to unjustified fibrinolysis. In the large fibrinolytic trials, percentages of nonconfirmed myocardial infarction range from 1.4% with stringent ECG criteria for acute myocardial infarction, to 23% in trials were no ECG confirmation was needed (Table 10.5-2).[12,16-23]

Table 10.5-2 Reports from the literature of unjustified thrombolysis

study year	patients	ECG criteria	unstable angina	unjustified thrombolysis	causes of unjustified thrombolysis
ASSET[17] 1988	5005	4	855 (17.1%)	556 (11.1%)	400 (7.9%): noncardiac causes 154 (3.1%): other causes 2 (0.04%): missing
TEAHAT[18] 1990	352	4	81 (23%)	14 (4.0%)	14 (4.0%): noncardiac causes
MITI[20] 1993	175 prehospital	1	5 (1%)	2 (0.5%)	1 (0.27%): pericarditis
	185 in-hospital	1			1 (0.27%): peptic ulcer
EMIP[21] 1993	2750 prehospital	2,3	206 (7.5%)	90 (3.2%)	9 (0.3%): pericarditis 6 (0.2%): aortic diss 25 (0.9%): other causes 50 (1.8%): noncardiac causes
	2719 in-hospital	2,3	184 (6.8%)	97 (3.6%)	12 (0.4%): pericarditis 3 (0.1%): aortic diss 32 (1.2%): other causes 50 (1.8%): noncardiac causes
GREAT[12] 1994	163 prehospital	4	n.a.	12 (7%)	59 (36%): nonspecific causes 12 (7%): normal ECG
	148 inhospital	4	n.a.	14 (10%)	45 (30%): nonspecific causes 14 (10%): normal ECG
GISSI[16] 1986	11712	2,3	328 (2.8%)	351 (3.0%)	351 (3.0%): MI not confirmed
TAMI[19] 1993	1387	1	8 (0.6%)	12 (0.9%)	4 (2.9%): early repolarisation 3 (2.2%): pericarditis 3 (2.2%): vasospasm 1 (0.07%): left ventricle hypertrophy 1 (0.07%): esophagitis
Khoury[22] 1996	609	2,3	20 (3.3%)	15 (2.5%)	8 (1.3%): noncardiac causes 3 (0.5%): pericarditis 2 (0.3%): pancreatitis 1 (0.2%): esophagitis 1 (0.2%): dissection
Schreiber[23] 2000	1077	5	28 (2.6%)	11 (1.0%)	6 (0.6%): other causes 5 (0.5%): pericarditis

legends: Ecg criteria see table 10.5-1

In these trials unstable angina, non-q myocardial infarction and pericarditis are the most common causes of unjustified fibrinolysis. It is important to note that in the early days of fibrinolysis unstable angina was not seen as a case of unjustified treatment. It is understandable that the highest percentage of unstable angina is in those trials treating patients without ECG documentation, and varies between 17 and 23%. Furthermore, none of these reports differentiate between unjustified fibrinolysis and aborted infarction, although the likelihood of the latter is mentioned.[12,21] It is possible that patients with aborted myocardial infarction are classified as having unstable angina in these trials. In the trials with ECG confirmation, the percentage of unstable angina ranges from 0.6 to 7.5%. Discarding unstable angina from those trials, the percentage of unjustified fibrinolysis ranges from 0.5% with ECG confirmation to 11.1% without ECG confirmation. Using only the trials with ECG diagnosis, the average percentage of unjustified fibrinolysis is 2.1%. Unlike our observations, pericarditis is here one of the most common diagnoses.

One of the reasons prehospital thrombolysis is not generally implemented may be the fear of unjustified fibrinolysis. Our data are supported by those from the literature,[12,21] showing that the risk of unjustified fibrinolysis is not significantly higher in a prehospital treatment group compared with in-hospital treatment. In contrast to the EMIP study[21], where ECG-diagnosis on the ambulance was made by a physician, and the GREAT study,[12] where no strict ECG criteria were used, our observations are close to current practice: prehospital assessment by nurses and in-hospital triage by physicians. Although unjustified fibrinolysis infarction is defined in our study on clinical grounds and thus clearly distinguished from aborted myocardial infarction, it will probably never be diagnosed with a 100% sensitivity and specificity in a strategy without immediate angiography. Assuming a risk of intracerebral hemorrhage of 1% and a risk of unjustified fibrinolysis of 5% the risk of hemorrhagic stroke will be 1 in 2000 prehospitally treated patients.[23] This risk is acceptable in comparison with complications of other medical interventions in life-threatening disorders.

There seems to be no reason to change the indications for fibrinolytic therapy, as currently used in cardiology practice and advocated by guidelines. For prehospital implementation computer diagnosis compares well with cardiologist-assisted diagnosis. This has also been confirmed in comparative ECG-studies.[8,9] Sensitivity for acute myocardial infarction varied between 53% and 81%,

depending of the amount of ST-elevation used. Specificity varied between 87% and 99%, depending on the amount of ST-elevation or reciprocal ST-segment depression used. Computers tend to have a lower sensitivity for anterior myocardial infarction than for inferior infarction and a lower sensitivity than cardiologist-assisted diagnosis,[9] possibly because some computer programs face problems in distinguishing early repolarisation from acute anterior myocardial infarction. When in doubt we adhere to the presence of reciprocal ST-segment depression[24] as a means for differentiating the ST-elevation of acute myocardial infarction from pericarditis or early repolarisation.

Limitations
The study was not randomized and not performed prospectively. Determination of serum troponins was not in routine use at the time the study was performed. This could have helped in establishing the difference in unjustified thrombolysis (normal values of CK, CK-MB and troponin) and aborted myocardial infarction (normal values of CK and possibly raised concentration of troponin), although no studies are available about the value of troponins for the diagnosis of abortion of acute myocardial infarction.

10.6 Conclusion

Using a prehospital strategy of diagnosing and treating acute ST-segment elevation myocardial infarction, we found a fourfold increase in abortion of myocardial infarction, compared with in-hospital treatment. Unjustified fibrinolytic therapy for acute myocardial infarction occurs as frequently in the prehospital as in the in-hospital setting. The use of different ECG methods for diagnosing acute myocardial infarction does not seem to make a difference. Our results in a nurse-ambulance setting are comparable with data from large trials with physician-initiated fibrinolysis. Most of our patients with incorrect fibrinolytic therapy in our database suffered from acute coronary syndrome, while in the literature unjustified therapy was mainly seen in patients with acute pericarditis. Aborted myocardial infarction, which in our data is associated with prehospital treatment and which can be seen as the ultimate goal of fibrinolytic therapy, must be differentiated from unjustified treatment.

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Abbreviations list

ECG	=	electrocardiogram
CAD	=	coronary artery disease
CPK	=	creatinin phosphokinase
CK-MB	=	creatinin phosphokinase-MB
ASAT	=	aspartate aminotransferase
ASSET	=	Anglo-Scandinavian Study of Early Thrombolysis
TEAHAT	=	The Thrombolysis Early in Acute Heart Attack Trial
TAMI	=	thrombolysis And Angioplasty in Myocardial Infarction
MITI	=	Myocardial Infarction Triage and Intervention
EMIP	=	European Myocardial Infarction Project
GREAT	=	Grampian Region Early Anistreplase Trial

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CHAPTER 11

COST-EFFECTIVENESS OF PREHOSPITAL THROMBOLYSIS

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11.1 Abstract

Background: The purpose of this study was to analyze the cost-effectiveness of prehospital thrombolysis compared with in-hospital thrombolysis.

Objectives: Prehospital thrombolysis in acute myocardial infarction is associated with a time gain of one hour in time to treatment. To guide budget allocations needed for prehospital treatment, a cost benefit analysis was made.

Methods: Two approaches were used: 1. The median time gain of prehospital thrombolysis, compared with in-hospital thrombolysis was matched with the associated risk reduction calculated on the basis of the literature. Costs of prehospital diagnosis and treatment were added to the survival after 30 days, and cost effectiveness was estimated as the additional costs due to prehospital thrombolysis divided by the number of life years gained. 2. A mathematical model was used to simulate patient histories, each drawn from a certain risk profile, whereby two histories were simulated for each patient, one with prehospital, and one with in-hospital treatment.

Results: In the first model, with a risk reduction of 30% for in-hospital, and 35% for prehospital treatment, prehospital treatment resulted in costs per life year gained at EUR 2,800. Using the second model, the average 30-day survival with prehospital thrombolysis was 93.73% compared to 93.32% with in-hospital thrombolysis. This results in an estimated cost per life year gained of EUR 1,837, assuming an average life expectancy of 10 years after being discharged.

Conclusion: Prehospital fibrinolysis costs EUR 1,800 to 2,800 per life year gained and seems, therefore, at least as cost-effective as other evidence-based infarct treatments.

11.2 Introduction

During the last decades, survival after acute ST-segment elevation myocardial infarction has improved substantially, partly related to the success of thrombolytic therapy. Time from symptom onset to treatment is one of the most important determinants of the success of thrombolytic therapy. If initiated within 1 to 2 hours after onset of symptoms 30-day mortality can be reduced by 40-50% as compared to placebo.[1] Several investigations have demonstrated that initiation of thrombolytic treatment prehospitally reduces treatment delay by about one hour.[2,3] Although considered safe and feasible, the strategy of prehospital diagnosis and treatment has not lead to widespread application.[4] Probably, one of the main obstacles is the organisation needed to implement such a strategy, implying fundamental changes such as budget-reallocations. The acceptance of a new program - with numerous financial implications - is best guided by a cost effectiveness analysis. This analysis should ideally be based on data from randomised trials that compare prehospital versus in-hospital treatment, with data collected on costs and effects. However, no such data are available. Moreover, large numbers of patients are needed to obtain sufficient power. Some simple calculations suggest that prehospital thrombolysis may lower 30-day mortality with an absolute reduction of 0.5 percent. This implies that one would need more than 30,000 patients per arm to show a significant mortality reduction with a power of 80%. Therefore, alternative approaches are needed and two are followed here. The first approach consists of a simple combination of some estimates, calculated as it were “on the back of an envelope”. In the second approach mathematical simulation techniques are applied, based on a combination of data from literature and detailed empirical data obtained in our local setting. The latter approach allows for many interdependencies between patient’s characteristics, survival probabilities and costs.[5]

In this report we performed a cost-effectiveness analysis, in which we used both approaches with data obtained from a detailed registration of time intervals of treatment of patients with acute myocardial infarction, with prehospital or in-hospital treatment.

11.3 Methods

Most estimates included in both approaches were based on data from 732 patients having acute ST elevation myocardial infarction: 468 patients treated in prehospital setting in Nijmegen during 1995-1999 and 264 patients treated inhospitally in the neighbouring city of Arnhem during 1995-1997. The city of Nijmegen has 150,000 inhabitants, and its two hospitals serve 240,000 inhabitants with 13 ambulances. The city of Arnhem has the same degree of urbanisation as Nijmegen, 140,000 inhabitants and the municipal hospital serves 240,000 inhabitants with 13 ambulances. The median time from onset of pain to arrival of ambulance (Nijmegen 78 minutes, Arnhem 88 minutes) and the median transport time of patients with acute myocardial infarction to the hospital (Nijmegen 10 minutes, Arnhem 11 minutes) do not differ significantly in these two cities. There was a 56-minute median time gain in patients treated prehospitally compared with in-hospital treatment, the first treated with a median of 89 minutes and the latter of 153 minutes. Except for the time to treatment both treatment groups were comparable according to age, sex, localisation of infarction, TIMI-risk score and 12 month follow up regarding treatment and mortality (table 11.3-1).

Table 11.3-1. Characteristics of all patients.

	Prehospital thrombolysis (Nijmegen) n = 468	In-hospital thrombolysis (Arnhem) n = 264	p
Age (mean) (years)	63	62	n.s.
Men, n (%)	322 (68)	190 (71)	
Minutes to treatment	97	153	p< 0.05
Transmural ischaemia, n (%)			
• anteroseptal	201 (44)	117 (44)	n.s.
• inferior	240 (51)	138 (51)	n.s.
• other	27 (6)	9 (3)	n.s.
TIMI-risk score at presentation	2.9	2.6	n.s.
Treatment 12 months, n (%)			
• Conservative	352 (75.2)	202 (76.5)	n.s.
• PCI (incl rescue PCI)	73 (15.6)	38 (14.4)	n.s.
• Bypass surgery	43 (9.2)	24 (9.1)	n.s.
Mortality at 12 months, n (%)	51 (10.9)	25 (9.5)	n.s.

I. "Back of the envelope" model

In the first approach, the one to be drawn simply "on the back of an envelope", the median delay from symptom onset to treatment in the setting of prehospital (Nijmegen) and in-hospital (Arnhem) thrombolysis were determined. Subsequently, the obtained 30-day mortality reduction as compared to placebo was estimated for both settings, applying data from the literature.[1,6,7] Costs associated with prehospital thrombolysis are those of implementing diagnosis systems in ambulances and base station, according to the financial administration of 2001. The effectiveness of prehospital thrombolysis over in-hospital treatment is calculated as the absolute difference in 30-day survival, multiplied with

an estimate of the average life expectancy, assumed to be 10 years after discharge.[8] Finally, the cost effectiveness of prehospital thrombolysis was estimated as the ratio between the additional costs and the absolute effects, expressed as the number of life years gained.

II. Simulation model

The "back on the envelope" calculation may lead to biased results for at least three reasons. The relation between treatment delay and treatment effect is supposed to be non-linear, so the estimated gains in life expectancy are relatively high in patients treated early (i.e. within 2 hours) after onset of pain, that is to say, a decrease from 4 to 2 hours is less effective than a decrease from 1 to 1/2 hour).[1] Consequently, when time gains are obtained in patients who present relatively late, survival gains on the basis on mean or median values may be overestimated. Secondly, survival gains are mainly obtained in high-risk patients, who tend to seek medical attention earlier than low-risk patients. In contrast, time gains are most easily obtained in patients presenting late after symptom onset, a cohort at relatively low risk. Then again, the benefits of prehospital thrombolysis may be overestimated by using means or medians. Thirdly, keeping high-risk patients alive may increase the average length of stay. This may increase costs with much more than just the costs of the home thrombolysis program. When taking all these aspects into account the balance between costs and effects may end up less favourably for home thrombolysis than when disregarding them.

Therefore, a more subtle approach was followed, using a mathematical model that simulates patient histories. Within this model the following phases were distinguished:

- The time from the onset of symptoms until treatment
- The time on the CCU until either death or discharge to the ward
- The time on the ward until discharge from the hospital
- The time from discharge until death

The model simulated 1,000,000 patient histories. Each patient history started with a certain risk profile, drawn from a distribution of certain risk-scores. Two histories were simulated for each patient, one assuming prehospital treatment

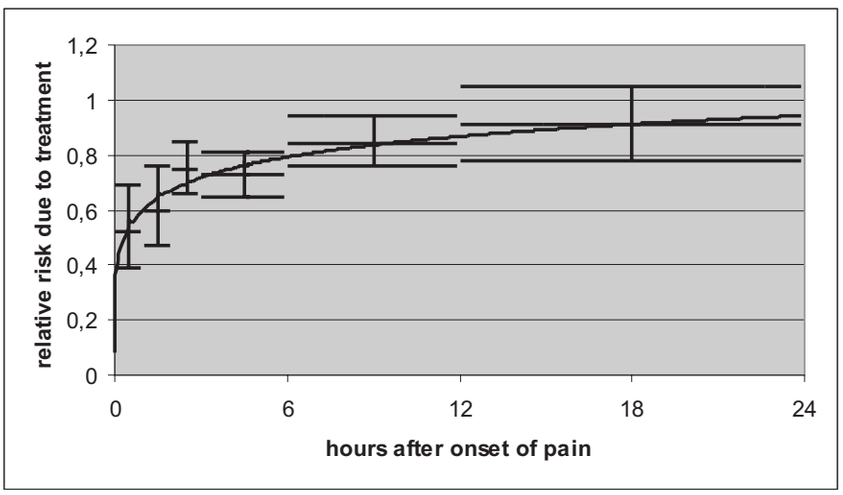
and one assuming in-hospital treatment. Subsequently, the patient is supposed to be treated at the CCU where he may either die or may be discharged alive. After the patient has left the CCU, treatment is supposed to be at the ward, followed by discharge alive. The dependencies that are taken into account are those between

a The risk score and the time to treatment
b The time to treatment and the risk of dying
c The risk of dying and the length of stay on the CCU
d The risk of dying and the length of stay on the ward

Using the history of the same patient in the hospital scenario, the simulation program started with a different distribution of time to treatment. All subsequent interdependencies were identical; all outcomes were of course different due to this different duration until treatment that effects all other durations and probabilities later onwards. Finally, after the patient has been discharged alive, he is supposed to live for 10 years[8] and no account is taken of a dependency between the patients' original risk score and survival after discharge.
For risk assessment data are used from the TIMI-risk score of ST elevation myocardial infarction.[9] Herein, certain parameters are weighed in such a way that age over 75 years and systolic blood pressure lower than 100 mm Hg is scored as 3 points, age from 65-74, heart rate more than 100 beats per minute and Killip class II-IV scored as 2 points and a anterior myocardial infarction, a history of prior infarction, hypertension and diabetes scored as 1 point. Allocation of 1 point to patients treated later than 4 hours was discarded, as patients are divided into groups treated before and after 2 hours in our assessment. Mortality at 30 days ranges from 0.9% with score 0 till 32.2% with more than 8 points.
The relationship between the TIMI risk score and time to treatment is investigated by comparing patients treated within and after two hours after the onset of pain and by Cox-regression analysis.
The distribution of the time from onset of pain to prehospital treatment is based on the data from Nijmegen. The distribution of the time from onset of pain to treatment in hospital is based on the data from Arnhem.
The initial risk of dying within 30 days without any thrombolytic therapy is based on this TIMI score and the corresponding survival probability as pub-

lished by Morrow et al.[9] These probabilities are multiplied with a factor 1.4* to correct for the fact that all patients in Morrows analysis had received thrombolytic therapy and that thrombolysis reduces the mortality risk with 0.3.
The effect of the time to treatment on 30-day survival is estimated using a 1-1 relationship between the time to treatment and the risk reduction in comparison to no thrombolytic treatment. This relationship is estimated based on the data as published by Boersma et al (figure 11.3-1).[1]

Figure 11.3-1. Relationship between relative risk and time to treatment. Derived from Boersma et al[1]



The days spent in the CCU and on the ward are analysed on the basis of data from Nijmegen for the prehospital treated patients and from Arnhem for the hospital treated patients. The relationship between the patients TIMI-risk score and the days spent on the CCU and on the ward is analysed using parametric survival models. Data are used from all patients treated in Nijmegen and Arnhem.

Cost-effectiveness

Costs are estimated per patient as the sum of the costs of the thrombolytic agent and the cost of in hospital treatment calculated as the length of stay multiplied with the unit costs per day on CCU and ward. In case of prehospital thrombolysis,

* factor 1.4 = 1 divided by (1-0.30)

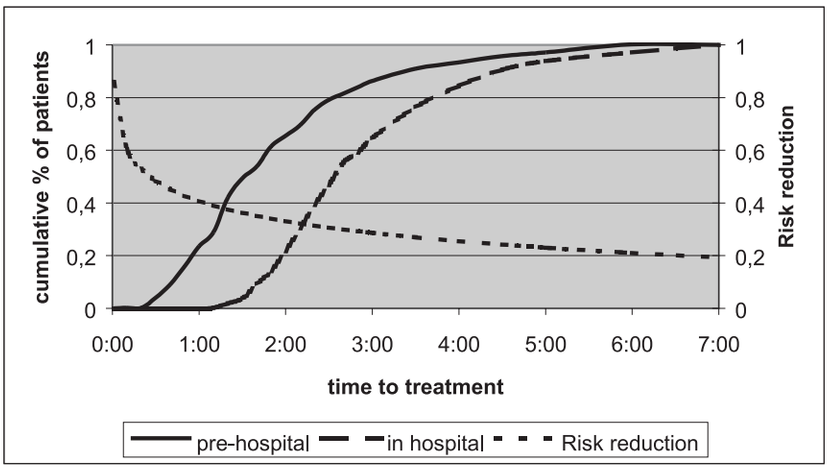
the costs of the infrastructure are added, assuming a programme of approximately 100 patients per year, and a service of 13 ambulances with crew.

11.4 Results

I. Mortality reduction by early treatment.

Figure 11.4-1 presents the relationship between time to treatment and corresponding relative risk in terms of the corresponding risk reduction in combination with the observed durations in Nijmegen and Arnhem. The median duration between onset of symptoms and in-hospital treatment (Arnhem) is 153 minutes (interquartile range) The delay between onset of symptoms and prehospital treatment (Nijmegen) is 89 minutes (interquartile range).

Figure 11.4-1. Risk reduction in relation to time to treatment, for in-and prehospital treatment. From Boersma *et al*[1]



II. "Back of the envelope" model

The 30-day relative mortality reduction by in-hospital thrombolysis compared to control therapy is estimated at 30%, whereas the relative mortality reduction by prehospital treatment is estimated at 35% (figure 11.4-1). Thus, assuming a 10% 30-day mortality rate after control therapy in-hospital treatment would reduce the risk to 7% and prehospital treatment to 6.5%. Therefore, assuming

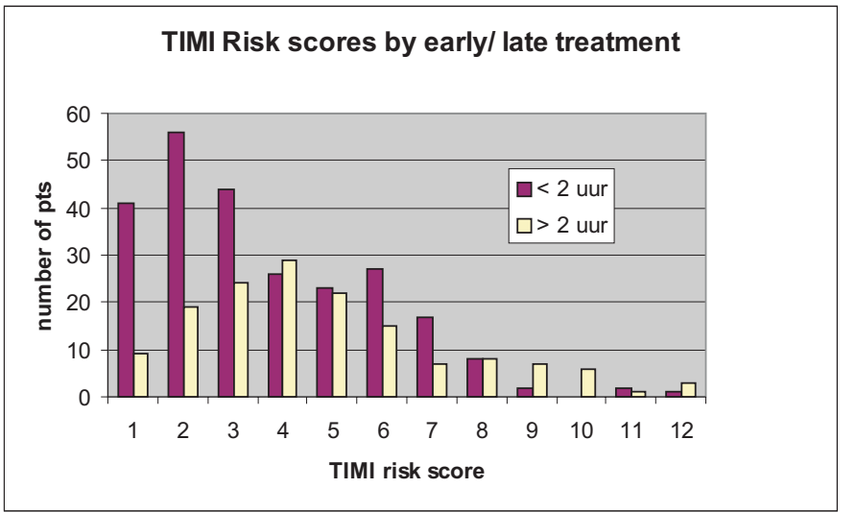
a life expectancy of 10 years after discharge, 5 additional life years would be gained per 100 patients treated. The additional costs of treating an annual number of 100 patients with prehospital thrombolysis can be estimated at EUR 70,000 per 5 years (implementing ECG-transmission systems on EUR 5,000 per ambulance and 13 ambulances, plus base station, assuming 5 year depreciation) or at EUR 14,000 per year. Consequently the costs per life year gained can be estimated at EUR 2,800.

III. Simulation model

Time to treatment and high risk

The simulation analysis starts with simulating patients with a distribution of TIMI scores. When developing the model it was hypothesised that high-risk patients would have a shorter time to treatment. However, using the prehospital treatment group, this could not be confirmed by a Cox regression analysis with time to treatment as the dependent variable and TIMI score as the explanatory variable. Figure 11.4-2 shows this, picturing the distribution of TIMI-score for patients treated before and after two hours after onset of the pain. Given the fact that no clear relationship could be identified between the time to treatment and TIMI score, we simulated time to treatment independent of the TIMI scores.

Figure 11.4-2. TIMI-risk score and time to treatment. See text



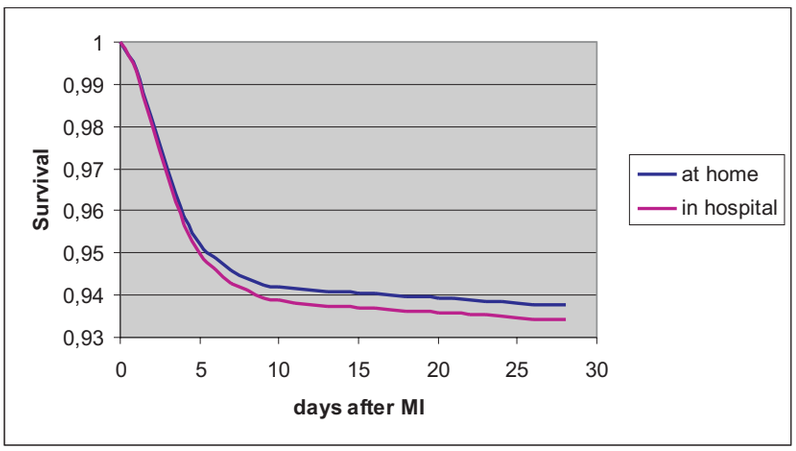
High risk and CCU/ward duration

A proportional hazards model assuming an exponential distribution addressed the relationship between the duration at the CCU and the duration at the ward. Running this model yielded the following estimates: patients with a TIMI score of 0 were estimated to stay 3.5 days on the CCU and 6.0 days on the ward. Hospital survivors with an initial TIMI score of 3 were estimated to stay 4.2 days on the CCU and 6.8 days on the ward, whereas those with an initial TIM score of 10 were estimated to stay 7.2 days on the CCU and 9.8 days on the ward. According to the model non-survivors died on the CCU after 4.3 days.

Prehospital thrombolysis and gain in 30-day survival

All results as presented above were implemented in our simulation model, which estimates 30-day survival with prehospital thrombolysis at 93.7% and with hospital thrombolysis at 93.3% (figure 11.4-3). As a result from our simulation analysis, it is estimated that prehospital thrombolysis will lead to 4.1 additional 30-day survivors per 1000 patients treated when compared to in-hospital treatment.

Figure 11.4-3. Expected 30 day survival according to simulation of 1.000.000 patients with in-hospital and prehospital treatment.



Estimates of costs can now be obtained by using the same costs as in our “back of the envelope” approach while estimating the costs of a CCU day at EUR 700

and the costs of a ward day at EUR 350. Table 11.4-1 presents the results in terms of resource use and costs, assuming a program of 100 patients per year. The results suggest that part of the initial investment of EUR 14,000 can be recouped by savings in relationship to a decrease in length of stay leading to a net annual cost of EUR 7350 for a prehospital thrombolysis program running for 100 patients, or 73500 for 1000 patients. The costs effectiveness is EUR 73500 divided by 4 survivors per 1000 patients treated equals to EUR 18,375. When assuming an average life expectancy of 10 years after being discharged, costs per life gained are EUR 1,837.

Table 11.4-1. Costs of prehospital diagnosis and treatment, compared with inhospital treatment, with 100 patients per year.

	Volumes		Unit cost	Costs	
	Prehospital	In- hospital		Prehospital	In hospital
Program costs	1	--	14,000	14,000	--
CCU days	417	424	700	291,900	296,800
Ward days	630	635	350	220,500	222,250
Total Costs				526,400	519,050

SENSITIVITY ANALYSIS

To some surprise, our simulation approach leads to almost the same estimates as our “back to the envelope” approach. Following the latter, it is relatively simple to analyse what effects are of different assumptions. Here there are only three variables of importance: the costs of the program, the effectiveness of prehospital thrombolysis and the life expectancy after being discharged alive. The question raised here is what estimates would lead to the conclusion that prehospital thrombolysis is not acceptable from a cost effectiveness point of view. For that purpose, we set the limit for cost effectiveness at EUR 20,000 per life year gained. First, there are the costs of the program. A 10% increase

in the costs would imply a 10% increase in the costs effectiveness ratio. So, one would need to estimate the annual program costs at EUR 100,000, instead of EUR 14,000 to reach to the limit of EUR 20,000 per life year gained. Such a high estimation would be rather implausible. Second, there is the estimate about effectiveness. Given the estimate of EUR 14,000 for the program and the estimate of the remaining life expectancy of 10 years, the reduction in 30 days survival would need to be 0.07% instead of 0.5% to reach the limit of EUR 20,000 per life year gained. Here it is noted that almost no doubt exists about the negative relationship that favours early treatment. Additionally, almost no doubt exists, looking at the Nijmegen experience, that prehospital thrombolysis leads to an earlier treatment. The question may than be how much earlier, and at what point in time. The risk reduction of 0.5% can as well be obtained by bringing the time to treatment back with almost an hour from 153 minutes to 97 (as in our case) as by a reduction of 30 minutes from 82 to 52 minutes.
Finally, doubts may exist about our estimate of a remaining life expectancy of 10 years after having been discharged alive. Given our other estimates, this life expectancy might decrease to less than 1 year and one would still end up with an estimate of the costs per life year gained that is under EUR 20,000.

11.5 Discussion

A prehospital thrombolysis program that decreases the median duration between the onset of symptoms and time to treatment with – on average – one hour, seems to result in a cost of EUR 1,800 to 2,800 per life year gained. Using the simulation analysis, patients stay on average 4.2 days at the CCU (95% interval 1.1-11.8) and 6.3 days at the ward (95% interval 0-15.4). Shorter length of stay was in favour of prehospital treatment. On the one hand, average length of stay increased in patients who would have died with hospital thrombolysis and are kept alive by prehospital treatment. On the other hand, length of stay decreases in patients who would survive their infarction after hospital thrombolysis, but whose mortality risk has decreased due to prehospital thrombolysis. The latter decrease consistently outweighs the first increase.

The GREAT study, a randomised trial of 163 prehospital treated patients versus 148 patients treated inhospitally, with a median time gain of 130 minutes,[10]

evaluated the cost effectiveness of prehospital thrombolysis. Costs were consisted of drug costs, training of general practitioners and their visits, and costs of electrocardiographs and defibrillators. With an additional probability of 0.11 of survival due to prehospital thrombolysis and a 4-year survival probability of 0.65 for hospital treatment and 0.76 for prehospital administration, the cost effectiveness ratio of prehospital thrombolysis was estimated at EUR 5,835 to EUR 12,000 per life saved.[11]
Capital expenditure and general practitioner's visits were not take into account, but included training for giving prehospital treatment, and of the costs of the drug. Training costs are difficult to assess and in our case is part of the usual refresher course of the ambulance crew. The costs of the drug (EUR 1,000) can be disregarded, because for cost effectiveness it does not matter where the drug is given, prehospital or in-hospital. Taking these costs into account, the GREAT results can be compared with our "back to the envelope" model.

Although the " back of an envelope" approach resulted in the same conclusion as the more sophisticated estimate, we thought the latter necessary for a variety of reasons. Firstly, a calculation of the costs and effects on the basis of averages may – in case of non-linear relationships – lead to biased estimates and account should be taken of the various heterogeneities. Secondly, one should realise that prehospital thrombolysis especially saves patients with high mortality risks at potentially high costs. So, not only the costs of the program should be taken into account but also the costs of the hospitalisation. Thirdly, the uncertainty surrounding the relationship between survival and the duration between the onset of symptoms and the time of treatment should be considered. Moreover, realising that the 'back of the envelope" calculation looks highly beneficial we thought it necessary to use conservative estimates. However, even then, a program with prehospital thrombolysis appears to have a very attractive economic profile. The question may then be raised why such an approach is not widely used. Here, some speculative reasons are put forward.

The first reason for the lack of widespread use might be found in the fact that the potential gain in time by treating patient's prehospitally depends on the current standards. According to the literature, the door to needle time in hospital may be substantial, 83 minutes when treatment is given at the CCU and 53

minutes when treatment is given in the emergency room. A recent survey even[12] showed that the delay between arrival of the patient at the hospital and starting of the treatment has not improved lately. It is still at least 40 minutes, suggesting that prehospital treatment is currently the best way to shorten delays. The potential gains, as well as the potential cost effectiveness, may depend on the organisation in the various hospitals. The better the current organisation, the better the cost effectiveness profile, the worse the organisation, the better the profile. So, one might come to the conclusion that the introduction of a prehospital thrombolysis program is like admitting that the current standards are sub-optimal.

A second reason may lie in the numbers needed to treat. Our conservative estimate implies that one has to treat about 125 patients prehospitally to save one additional life. On average general practitioners see 2 to 3 patients with acute ST elevation myocardial infarction per year and may feel that they have to continue practice for more then 40 years before they save one life. This may not look very worthwhile, and they - maybe supported by the situation and the relatives of the patient - may feel more comfortable by referring these patients to hospital as fast as possible.

A third reason may be found in the costs and organisation. One needs to install ambulances and a department of cardiology with the necessary equipment and moreover, one needs to equip the ambulances with thrombolysis agents. This asks for education and communication with ambulance staff and general practitioners, and reallocations of budgets.

Study limitations

The estimates of the simulation model are based on the risk score of the TIMI-study. This risk score excluded cardiogenic shock, systolic and diastolic hypertension and history of stroke. Because these are not necessarily exclusion criteria in prehospital thrombolysis one includes patients with a potential high risk of death or complications, balancing the cost effectiveness in a less desirable way.

The true natural history and 10-year survival of acute myocardial infarction is difficult to assess, because more than half of the deaths occur outside hospital,

with uncertain causes of death and with unreliable death certificates. An average survival after discharge of 10 years is certainly not a high estimate, with the cost per life year gained even lower if the real survival would indeed be longer.
Ideally, one would have used data from patients randomised in prehospital or in-hospital thrombolysis. However, with the numerous results of the importance of early treatment, this is not ethically justifiable. So we used the data of patients treated in one city (Nijmegen) prehospitally, and in another city (Arnhem) inhospitally. The Arnhem situation is comparable to that of Nijmegen in terms of population, degree of urbanization, transport times for ambulances and CCU-facilities, the key difference being that no pre-hospital treatment was available in Arnhem during the period of the study. This, together with the fact that both patient groups reveal baseline characteristics in reasonable agreement with those occurring in the literature, we expect them to be comparable. In doing so one approximates an unblinded randomisation as best as possible, accepting the difference patient care of the two cities.

11.6 Conclusion

Prehospital thrombolysis seems to be cost effective: EUR 2,800 per life gained using a simple calculation method of risk reduction associated with early treatment. When a more sophisticated mathematical model using patient's histories and risk profiles is used the result is an estimate of EUR 1,837 per life year gained. The balance between the costs and effects seems attractive and our conclusion is that hospitals, general practitioners and health care authorities should support a widespread use of prehospital thrombolysis.

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CHAPTER 12

SUMMARY AND CONCLUSIONS

12.1 Summary

Fifteen years of experience in prehospital thrombolysis for acute ST elevation myocardial infarction in our region has formed the basis of this thesis, together with data from Rotterdam, one of the other centres applying this strategy, and with data from Zwolle, where prehospital triage and primary angioplasty is practised.

Chapter 1. Introduction
The questions this thesis tries to answer are threefold.
Firstly, questions are answered, which are all related to the importance of time to treatment: the time gain of a prehospital strategy, the difference in time gain using bolus or infusion thrombolytics and the reduction of 30-day mortality and heart failure. Secondly, the concept of aborted myocardial infarction is investigated in prehospital thrombolysis, in in-hospital thrombolysis and in primary angioplasty with prehospital triage. Furthermore, linked with aborted myocardial infarction, attention is given to unjustified fibrinolysis, both in the Nijmegen and the Rotterdam experience and in the literature. Thirdly, some practical aspects of prehospital thrombolysis are reviewed, focusing on its costs and effectiveness.

Chapter 2. Overview
The acute coronary syndrome for which treatment with thrombolytics is indicated is characterized by ST-segment elevation on the electrocardiogram. It is defined by typical symptoms, ECG-signs of transmural ischaemia (ST-segment elevation), development of Q-waves on the ECG, and signs of myocardial cell death, as reflected by the rise of typical biochemical markers. The latter characteristic can be absent, if treatment is given in such a way that cell death is averted, and this is called in this thesis an *aborted* myocardial infarction. An acute ST elevation myocardial infarction is *suspected*, and thus followed by treatment; if after serial ECG's and measurement of biochemical markers the diagnosis was correct, the infarction is *proven* or *established*. If the results of serial measurements of biochemical markers is less than two times the upper value, the infarction is *aborted*. In both cases the treatment was justified. If the diagnosis after serial ECG's and biochemical markers appeared to be incorrect, the treatment was unjustified.

In the last 25 years much research has been done to salvage ischaemic myocardial tissue. The overall conclusion is that time is of utmost importance. This has been demonstrated in animal experiments, by inducing myocardial ischaemia followed by interventions at various time intervals, and by analysing time to treatment after onset of symptoms in the first published trials with acute ST elevation myocardial infarctions and thrombolytic therapy. From the late eighties of the last century onwards, reports have been published about the feasibility of diagnosing acute myocardial infarction prehospitally, with the introduction of the administration of fibrinolysis before the patient is transported to the hospital. Since the first publication by Gotsman many reports about early and prehospital thrombolysis have been published. Pivotal for this thesis were the results of Boersma's meta-analysis of early thrombolytic treatment, in which treatment within 1 hour after onset of symptoms appeared to reduce mortality more than expected as treatment later than 1 hour. This resulted in the "Golden Hour" of treatment, and laid the foundation of the concept of aborted myocardial infarction. Boersma concludes that the assessment of prehospital treatment is likely to be better by dividing all patients (prehospital and hospital) in an early and a late treatment group, rather than comparing prehospital with in-hospital patients. Comparing only in-hospital treated patients yields too few patients to compile an early treatment group, as only an average of 6% of in-hospitally treated patients are treated within 1 hour. Prehospital thrombolysis is thus the only way to collect a 1- and 2-hour treatment group large enough to make such an assessment possible.

Chapter 3. Study of Time Intervals in Myocardial Ischaemic Syndromes (STIMIS)

In the STIMIS-study the various points in time of every event between onset of chest pain and completed hospital admission were assessed in 1,152 patients with chest pain of possible cardiac origin. This study was part of the Nijmegen Home Thrombolysis Program. Of these patients 200 were actually treated with thrombolytic therapy: 141 at home and 59 after hospital arrival. After final analysis, 393 patients proved to have myocardial infarction. In comparison with the whole group of patients with chest pain, the time points of every event occurred earlier in patients with myocardial infarction. There was a median time interval of 89 minutes between onset of symptoms and treatment in

patients treated prehospitally, and 152 minutes in patients treated in-hospitally. Of the prehospital thrombolysis group 28% of the patients and of the hospital thrombolysis group no patients were treated within one hour. Within two hours these values were 65 and 25%, respectively.

Chapter 4. Registration of symptom onset-to door and door-to-needle times in 4 hospitals outside the Nijmegen region
To facilitate discussions about the need for prehospital thrombolysis in regions other than Nijmegen, where such a strategy already exists, in-hospital time intervals of diagnosing and treating patients with chest pain have been collected and an estimation of percentages of patients that can be treated within 2 hours with this strategy have been made. In 4 regional hospitals around the city of Nijmegen time intervals were noted on a special form. To calculate the time gain prehospital treatment could have provided in the 4 regions to the median time from onset of pain to arrival of the ambulance 27 minutes was added, which is the time it takes in Nijmegen to diagnose and treat the patient in a prehospital strategy. Door-to-needle times in the 4 regions varied between 39 and 50 minutes and are comparable with the 48 minutes of in-hospital treatment in Nijmegen. Total time to treatment varied between 145 and 167 minutes. If a prehospital strategy had been present, there would have been a time gain in the 4 regions varying between 32 and 51 minutes, resulting in 55% patients treated within 2 hours instead of the current 25%. In conclusion, with a prehospital strategy the 4 regions could reduce the time to treatment, resulting in doubling the number of patients treated within 2 hours.

Chapter 5. Time from symptom onset to treatment and outcome in prehospital thrombolysis for acute myocardial infarction
Because the prehospital thrombolysis program has created a considerable database of patients treated within 1 and 2 hours after symptom onset, we analyzed this database in search for patients' characteristics with a better outcome in the early treatment group. From 1994 to 2000 a total of 475 patients were treated because of acute myocardial infarction using prehospital administration of anistreplase (in 407 patients) or reteplase (in 68 patients) after diagnosis was confirmed with transtelephonic transmission of the ECG. There was no age limit. The patient data were divided into 2 groups: one with treatment within 2

hours after onset of pain, and one treated later than that. Thirty-day mortality and symptoms and clinical signs of heart failure were used as parameters of outcome. Both univariate and stepwise logistic regression analyses were used to test 30-day mortality against age, actual time to treatment, prior myocardial infarction, hypertension, diabetes, hyperlipidamia, anterior myocardial infarction, Killip class, systolic blood pressure and heart rate at presentation. Overall 30-day mortality was 9.0%. Overall heart failure was in 16.4% of patients. Both mortality (5.5% vs. 15.2%, $p<0.02$) and heart failure (12.7% vs. 23.2%, $p<0.02$) were significantly lower in the early treatment group compared to the group treated late. Independent parameters showing a relation with 30-day mortality were age, time to treatment, hypertension and prior myocardial infarction. Age, time to treatment, hypertension and hyperlipidaemia were identified as predicting heart failure within the first 30 days. In conclusion, prehospital thrombolysis results in about two thirds of patients being treated within 2 hours after onset of symptoms. Independent variables for 30-day mortality were age, hypertension, prior myocardial infarction and time to treatment. Age, hypertension, hyperlipidaemia and time to treatment were independent predictors for heart failure.

Chapter 6. Effect of prehospital thrombolysis on aborting myocardial infarction
Hypothesizing that aborted ST elevation myocardial infarction is associated with prehospital thrombolysis a comparison was made between prehospital and in-hospital treated patients. A total of 227 patients were treated in the prehospital setting (bolus anistreplase i.v.) and compared retrospectively with those of 269 patients who underwent in-hospital thrombolytic therapy (1.5 million units of intravenous streptokinase or 100 mg of intravenous recombinant tissue plasminogen activator (rt-PA) and intravenous heparin) in the same period in a nearby hospital not using a prehospital thrombolysis program. The diagnosis of aborted myocardial infarction was made for both groups if 1) the combination of chest pain and transient electrocardiographic changes suggested transmural ischaemia and 2) if a rise in creatine kinase and its iso-enzym > 2 times the normal value failed to appear, and 3) the cumulative ST-segment elevation and depression decreased to less than 50% within 2 hours of treatment. Unjustified treatment was excluded in 3 prehospital and 5 in-hospital patients. A total of 30 of the 224 patients (13.4 %) of the prehospital group and 12 of the 266 (4.5 %)

in-hospital group thus fulfilled the criteria for an aborted myocardial infarction ($p < 0.05$). None of these patients of either group died during their stay in hospital or before the follow up at 12 months.

Chapter 7. Extended studies on aborted myocardial infarction in reperfusion therapy

Using an extended database we investigated the timespan, in which abortion of myocardial infarction can be expected and the differences in parameters of aborted compared to established ST elevation myocardial infarction. From patients suspected of acute myocardial infarctions ECG's were transmitted by the ambulance service to the coronary care units of one of the Nijmegen hospitals. After confirmation of myocardial infarction 475 patients were included and treated with thrombolysis before transport. Their data were retrospectively compared with those of 269 patients treated in hospitally with streptokinase or rt-PA in a nearby hospital without a prehospital thrombolysis program. A stepwise regression analysis was used to test independent predictors for abortion of myocardial infarction. After correction for unjustified thrombolysis 80 patients (17.1%) of the 468 prehospital treated patients and 12 (4.5%) of the 264 in-hospital treated patients fulfilled the criteria of aborted myocardial infarction. There was no difference in age, sex, risk factors, and location of infarction of aborted myocardial infarction compared to established ST elevation myocardial infarction. More than 30% of these abortion infarction patients who underwent angiography had 2- or 3-vessel disease. Apart from time to treatment, which was significantly shorter in the patients with aborted myocardial infarction, a lower ST-segment elevation and a higher incidence of pre-infarction angina were independent predictors for abortion of myocardial infarction. The prognosis of patients with aborted myocardial infarction is significantly better compared with established myocardial infarction: 12 month mortality of 2.2% and 11.6% respectively. In conclusion, prehospital thrombolysis is more often associated with abortion of myocardial infarction when compared to in-hospital treatment. A shorter time to treatment, a lower amount of ST elevation and a higher incidence of pre-infarction angina were predictors of abortion of myocardial infarction.

Chapter 8. Primary angioplasty or prehospital thrombolysis and abortion of myocardial infarction

Combining prehospital infarct triage with angioplasty has reduced symptom-to-balloon times considerably. Reperfusion times with primary angioplasty with prehospital triage were compared to prehospital thrombolysis. The incidence of aborted myocardial infarction was assessed in groups of patients treated with either strategy. A total of 545 patients were treated prehospitally in the cities Rotterdam and Nijmegen and compared with 236 patients treated with primary angioplasty after prehospital triage in Zwolle. All patients were treated with nitroglycerine and aspirin, and those prior to angioplasty with heparin i.v. Prehospital therapy consisted of streptokinase or anistreplase in Nijmegen or Rotterdam before transport. Time to reperfusion is defined as symptom to balloon time in primary angioplasty or symptom to thrombolysis plus 60 minutes in prehospital thrombolysis. Aborted myocardial infarction was present in 16% of the prehospital thrombolysis patients and 11% in the primary angioplasty with prehospital triage group. In primary angioplasty, reperfusion time categorised as earlier and later than 2 hours, showed a significantly higher incidence of aborted myocardial infarction in the early treated group. Mortality of 30-days is not significantly different in both early and late angioplasty and early and late prehospital thrombolysis, and in comparison of both treatment strategies.

In conclusion, both prehospital thrombolysis and primary angioplasty with prehospital triage is associated with abortion of myocardial infarction, showing comparable reperfusion times. In the case of primary angioplasty a significantly higher incidence of aborted myocardial infarction is seen in patients treated within 2 hours after symptom onset.

Chapter 9. Prehospital thrombolysis with reteplase; the Nijmegen/Rotterdam study

An observational study was performed to assess time to treatment and clinical parameters of double bolus reteplase compared to current therapy with streptokinase or bolus anistreplase in two cities (Rotterdam and Nijmegen) in the Netherlands. Reteplase or anistreplase/streptokinase was assigned to patients according to order of presentation. All patients were treated with nitrates sublingually and aspirin orally. In total 250 patients were treated between April 1, 1999 and August 1, 2000. Reteplase was used in 120 patients and anistre-

plase/streptokinase in 130 patients. Using double bolus reteplase resulted in a significantly shorter time of treatment of a median of 81 minutes compared to a median of 104 minutes with the established therapy ($p<0.05$). There were no differences in mortality, aborted myocardial infarction, hemorrhagic stroke and the need for rescue angioplasty in both groups. Within 2 hours 64% of patients were treated.
In conclusion, in prehospital thrombolysis double bolus reteplase is associated with a shorter time to treatment than bolus anistreplase or infusion of streptokinase.

Chapter 10. Prehospital versus hospital fibrinolytic therapy using automated versus cardiologist ECG diagnosis of myocardial infarction: abortion of myocardial infarction and unjustified fibrinolytic therapy.
The purpose of this study was to investigate the percentages of unjustified fibrinolytic therapy in prehospital settings in The Netherlands using different means of diagnosing myocardial infarction. Unjustified fibrinolysis for presumed acute ST elevation myocardial infarction can be disastrous, but must be differentiated from justified thrombolysis resulting in aborted myocardial infarction. In the city of Rotterdam 118 patients were prehospitally treated for myocardial infarction, diagnosed using a mobile computer ECG; in the city of Nijmegen 132 patients were treated prehospitally, using transtelephonic transmission of the ECG to the CCU and judged by a cardiologist. Their data were compared with those of 269 patients treated in-hospital in the city of Arnhem, using the same ECG-criteria. Abortion of myocardial infarction was diagnosed in the absence of a significant rise in cardiac enzymes and in the presence of resolution of 50% of ST-segment deviation within 2 hours after onset of therapy. Lacking these, the diagnosis of unjustified fibrinolytic therapy was made. Unjustified treatment occurred in 8 prehospitally treated patients: 4 in Rotterdam (3.3%), 4 in Nijmegen (3.0%) and in 5 (1.9%) of the in-hospitally treated patients in Arnhem. Aborted myocardial infarction occurred in 14.4% and 17.4% in Rotterdam respectively Nijmegen against 4.5% in in-hospital treatment in Arnhem ($p<0.001$). In conclusion, although unjustified fibrinolysis for acute myocardial infarction is undesirable, it occurs in the same frequency in prehospital as in in-hospital settings. The use of different ECG methods for diagnosing acute myocardial infarction does not seem to make any difference

Chapter 11. Cost-effectiveness of prehospital thrombolysis

The purpose of this study was to analyze the cost-effectiveness of prehospital thrombolysis compared with in-hospital thrombolysis. Although prehospital thrombolysis in acute myocardial infarction is associated with a time gain of one hour in time to treatment, this strategy has not lead to widespread application. To guide budget allocations needed for prehospital treatment, a cost benefit analysis was made of this treatment strategy. Two approaches were used: in one method the median time gain of prehospital thrombolysis, compared with in-hospital thrombolysis was matched with the associated risk reduction calculated on the basis of the literature. Costs of prehospital diagnosis and treatment were added to the survival after 30 days, and cost effectiveness was estimated as the additional costs due to prehospital thrombolysis divided by the number of life years gained. In the other method a mathematical model was used to simulate patient histories, each drawn from a certain risk profile, whereby two histories were simulated for each patient, one with prehospital, and one with in-hospital treatment. The time intervals were based on data of 736 patients with acute myocardial infarction, 468 patients prehospitally and 268 patients in hospitally treated. For risk assessment, data were used from the TIMI-risk score of ST-segment elevation myocardial infarction.

In the first model, with a risk reduction of 30% for in-hospital, and 35% for prehospital treatment, prehospital treatment resulted in costs per life year gained at EUR 2,800. Using the second model, simulation of patient histories and according risk profiles, the average 30-day survival with prehospital thrombolysis was 93.73% compared to 93.32% with in-hospital thrombolysis. This results in an estimated cost per life year gained of EUR 1,837, assuming an average life expectancy of 10 years after being discharged. In conclusion, prehospital thrombolysis seems cost-effective: EUR 1,800 to 2800 per life year gained which compares well with other evidence-based therapies in acute myocardial infarction.

12.2 Conclusions

We can now answer the questions we set out in the introduction of this thesis.

1. Time to treatment in ST elevation myocardial infarction is 152 minutes in Nijmegen and varies between 145 minutes and 160 minutes in other regions. Prehospital thrombolysis in Nijmegen results in a time to treatment of 89 minutes with a median time gain of 63 minutes. With prehospital thrombolysis 28% of patients could be treated within 1 hour and 65% within 2 hours, and 25% of in-hospital treated patients within 2 hours. Between 32 and 51 minutes could be gained if a prehospital strategy would have been present in the other regions.
2. Both mortality and heart failure were significantly lower in the early treatment group (treatment within 2 hours) compared to the group treated late (treatment later than 2 hours). Independent parameters showing a relation with 30-day mortality were age, time to treatment, hypertension and prior myocardial infarction. Age, time to treatment, hypertension and hyperlipidaemia were identified as predicting heart failure within the first 30 days. Aborted myocardial infarction is diagnosed in 17% of the prehospital treated patients and 4.5% of in-hospital treated patients, and is associated with a significantly better 12-month mortality than established myocardial infarction (2.2% and 11.6% respectively).
3. Abortion of myocardial infarction is not confined to prehospital thrombolysis, but can also be achieved using primary angioplasty with prehospital triage. The incidence of abortion of myocardial infarction is significantly higher in patients treated within 2 hours with primary angioplasty compared with patients treated later.
4. Using newer generation bolus therapy in a prehospital strategy is associated with a significantly lower time to treatment as compared with a current therapy of infusion of streptokinase or bolus anistreplase.
5. The incidence of unjustified fibrinolysis in prehospital therapy, using 2 different ways of diagnosis, compares well with in-hospital false diagnosis.
6. Prehospital thrombolysis is very cost-effective: EUR 1,800 and EUR 2,800 per life year gained and compares very well with other evidence-based therapies in acute myocardial infarction.

12.3 Future aspects

Prehospital thrombolysis

This thesis shows that prehospital administration of thrombolytic therapy is essential in shortening time to treatment of acute ST elevation myocardial infarction. However, implementation of such a strategy still encounters various obstacles:

- Contrary to in-hospital thrombolysis, a prehospital strategy asks a considerable investment, both in organisation of other parties, like general practitioners and ambulance staff, and in money.
- Many health workers, especially members of hospital staff, do not realize the delays in treatment. They underline the importance of rapid transport to the hospital, and do not notice the substantial door-to-needle time in hospital.
- Fear of unjustified thrombolysis in a prehospital setting.
- Lack of a consensus of treatment of acute myocardial infarction with thrombolysis or primary angioplasty, which divides large regions with preferences for one therapy, thus delaying implementation of prehospital thrombolysis.

Prehospital triage

This thesis, combined with the literature, underline the importance of time in the treatment of the acute ST elevation myocardial infarction. Prehospital diagnosis paves the way for prehospital thrombolysis or prompt primary angioplasty. It is advisable to organize prehospital triage regionally, in cooperation with the regional ambulance service, the local and referral hospitals in that region and the district association of general practitioners. The Netherlands Society of Cardiology holds this view and included prehospital triage and thrombolysis in their recently updated guidelines. In our fifteen years experience of prehospital thrombolysis the cooperation of local general practitioners was very important, especially in the Nijmegen region where general practitioners play a large role in the first consultation of patients with chest pain and where little self-referral of patients to emergency departments exists. Furthermore, the ambulance staff, more than many hospital and health authorities, was conscious of the delays of patients with chest pain, and therefore was

willing to expand their responsibility of diagnosing and treating acute ST elevation myocardial infarction before transport to the hospital. Thus, the implementation of a prehospital strategy can only be successful if it is done in cooperation with local general practitioners and ambulance services.

Prehospital thrombolysis or primary angioplasty

Many studies comparing in-hospital thrombolysis with primary angioplasty show advantages for the latter.[1] However, the last word on this subject has not been written, especially considering the results from recent studies [2,3] where prehospital thrombolysis, combined with rescue angioplasty, is compared to primary angioplasty. It seems that the time to reperfusion dictates the outcome and not the means of realizing this; in other words, if the time to reperfusion using either angioplasty or thrombolysis becomes similar, it is expected that the benefit of thrombolysis becomes comparable to the benefit of angioplasty. Furthermore, newer thrombolytic agents have been developed, facilitating prehospital administration considerably, with additional reduction in treatment delays. In addition, reduced-dose thrombolytic therapy in combination with the administration of a potent antiplatelet agent like a glycoprotein IIb/IIIa inhibitor restores antegrade flow at least as effectively as full-dose thrombolytic therapy, but is associated with a lower rate of reinfarction.[4] This combined approach seems likely to reduce reocclusion.[5,6,7] Finally, in the case of facilitated primary angioplasty, this will mean prehospital triage, administration of a thrombolytic, GP IIb/IIIa or its combination and transport to an expert regional catheterization facility; in the case of thrombolysis it will mean prehospital diagnosis and treatment.

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SAMENVATTING EN CONCLUSIES

De basis van deze dissertatie wordt gevormd door de ervaring, die is opgedaan in Nijmegen met 15 jaar prehospitale trombolyse van het acute ST elevatie myocardinfarct. Daarnaast zijn gegevens gebruikt afkomstig uit Rotterdam, één van de andere centra in Nederland waar ervaring met prehospitale trombolyse is opgedaan, en uit Zwolle, waar een strategie bestaat met prehospitale triage en primaire angioplastiek.

Hoofdstuk 1. Inleiding

Deze dissertatie probeert drie vraagstellingen te beantwoorden. In de eerste plaats worden vragen beantwoord die allemaal te maken hebben met het belang van vroege behandeling van het acute myocardinfarct: de tijdwinst van een prehospitale strategie, het verschil in tijdwinst wanneer bolus- dan wel infusietherapie wordt gebruikt en de reductie in de mortaliteit na 30 dagen en de ontwikkeling van hartfalen bij vroege behandeling. In de tweede plaats wordt het concept van het verijdelde infarct onderzocht, zoals dit zich voordoet bij prehospitale trombolyse, bij in-hospitale trombolyse en bij primaire angioplastiek met prehospitale triage. Verder wordt aandacht gegeven aan onterechte behandeling, hetgeen onlosmakelijk verbonden is met het concept van het verijdeld infarct; dit is onderzocht in de Nijmeegse en Rotterdamse prehospitale patiëntengroep en in de trombolyse-literatuur. In de derde plaats zijn praktische aspecten van prehospitale trombolyse onderzocht, waarbij de nadruk werd gelegd op kosten en effectiviteit.

Hoofdstuk 2. Overzicht

Het acute coronaire syndroom waarvoor behandeling met trombolyse is geïndiceerd wordt gekenmerkt door ST-segment elevatie op het elektrocardiogram. Het wordt gedefinieerd door typische symptomen, ECG-tekenen van transmurale ischaemie (ST-segment elevatie), de ontwikkeling van Q-golven op het ECG, en tekenen van myocardcelnecrose, hetgeen wordt gekarakteriseerd door de stijging van bepaalde enzymconcentraties in het bloed. Het laatste kenmerk kan afwezig zijn, en wel indien de therapie zodanig is ingesteld

dat celdood wordt verijdeld; in deze dissertatie wordt dit een verijdeld infarct genoemd (*aborted myocardial infarction*). Een acuut ST elevatie myocard infarct wordt vermoed (*suspected*) en op grond van dit vermoeden behandeld. Indien na beoordeling van meerdere ECG's en bloedbepalingen van myocard-enzymen de diagnose correct is, noemen we het infarct bewezen of bevestigd (*proven, established*). Indien de enzymbepalingen de waarde van tweemaal de bovengrens van normaal niet overschrijdt noemen we het infarct verijdeld (*aborted*). In beide gevallen was de behandeling terecht (*justified*) toegediend. Indien de diagnose na het beoordelen van meerdere ECG's en bepalingen van myocardenzymen incorrect blijkt te zijn, spreken we van onterechte (*unjustified*) therapie.
In de laatste 25 jaar is veel onderzoek verricht naar methoden om ischaemisch myocard te redden van celdood. Uiteindelijk bleek de tijd van begin van de symptomen tot behandeling van het allergrootste belang te zijn. Dit werd gedemonstreerd in het diermodel, waarbij ischaemie werd geïnduceerd, gevolgd door interventies om de ischaemie weer op te heffen op verschillende momenten na de ischaemie-inductie. Verder toonden de eerste gepubliceerde trials met trombolyse versus placebo het belang aan van vroege behandeling. Vanaf de jaren tachtig van de vorige eeuw zijn studies verschenen over prehospitale trombolyse, waarin de uitvoerbaarheid van prehospitale diagnostiek, gevolgd door trombolyse vòòrdat de patiënt op transport naar het ziekenhuis werd gesteld, werd bevestigd. Sinds de eerste publicatie van Gotsman hebben vele studies over vroege en prehospitale trombolyse het licht gezien. Van groot belang voor deze dissertatie waren de resultaten van een meta-analyse van Boersma over vroege behandeling, waarin de start van de trombolyse binnen 1 uur na begin van de klachten de mortaliteit veel meer wist te verlagen dan werd verwacht. Boersma onderstreepte het belang van "het gouden uur" van infarct-behandeling en zijn meta-analyse dient als basis voor het concept van het verijdelde infarct. Boersma concludeerde dat het voor het beoordelen van de voordelen van prehospitale trombolyse essentieel is alle patienten (zowel inhospitaal als prehospitaal behandeld) te verdelen in een vroege en een laat-behandelde groep, en niet door prehospitale patiënten te vergelijken met ziekenhuispatiënten. Indien men die verdeling alleen met in-hospitaal behandelde patiënten zou doen, dan is de groep vroeg behandelden veel te klein, daar immers niet meer dan 6% van de in-hospitaal behandelde patiënten binnen 1

uur wordt getrombolyseerd. Prehospitale trombolyse is de enige manier om een groep patiënten samen te stellen die binnen 1 à 2 uur behandeld is en die groot genoeg is om een dergelijke analyse mogelijk te maken.

Hoofdstuk 3. Tijdsintervallen studie (STIMIS)
In de STIMIS-studie werden verschillende momenten in de tijd tussen begin van de symptomen tot opname in het ziekenhuis beoordeeld, en wel in 1152 patiënten met verdenking op een acuut coronair syndroom. Deze studie was onderdeel van het Nijmeegse thuistrombolyse project. Van deze patiënten werden er uiteindelijk 200 behandeld met trombolyse: 141 prehospitaal en 59 na opname in het ziekenhuis. In de uiteindelijke analyse werd bij 393 van deze 1152 patiënten een infarct bevestigd. In vergelijking met alle patiënten bleken diegenen met een bevestigd myocardinfarct vroeger te worden behandeld. Er was een mediaan tijdsinterval van 89 minuten tussen begin van klachten en behandeling bij prehospitale trombolyse en 152 minuten bij patiënten die in-hospitaal werden behandeld. Van de prehospitale patiëntengroep bleek 28% te zijn behandeld binnen 1 uur, tegen geeneen van de in-hospitale groep. Binnen 2 uur was 65%, respectievelijk 25% van de patiënten behandeld.

Hoofdstuk 4. Registratie van de tijdsintervallen tussen begin van de symptomen en start van de behandeling in 4 ziekenhuizen buiten de regio Nijmegen
Teneinde te beoordelen of in regio's buiten Nijmegen prehospitale trombolyse van nut zou zijn, werden in-hospitale tijdsintervallen van diagnose en behandeling verzameld van patiënten met pijn op de borst, waarmee een schatting kon worden gemaakt van het percentage van patiënten dat binnen 2 uur zou kunnen worden behandeld indien een prehospitale behandeling in deze regio's aanwezig zou zijn geweest. Om de tijdwinst van mogelijke prehospitale behandeling in deze 4 regio's uit te rekenen werd 27 minuten toegevoegd aan de tijd vanaf aankomst van de ambulancedienst. Deze 27 minuten is de tijd die de ambulancedienst in Nijmegen nodig heeft om de diagnose myocardinfarct te stellen en om prehospitale trombolyse te geven. De tijd tussen aankomst van de ambulance in het ziekenhuis en behandeling aldaar (*door-to-needle time*) varieerde van 39 tot 50 minuten in deze 4 regio's en is dus vergelijkbaar met de 48 minuten in de Nijmeegse ziekenhuizen. De totale behandelingsduur varieerde van 145 tot 167 minuten. Indien een prehospitale behandeling aan-

wezig zou zijn geweest, dan zou er een tijdwinst van 32 tot 51 minuten zijn, waarbij 55% van de patiënten binnen 2 uur zou kunnen worden behandeld in plaats van de huidige 25%. Concluderend, prehospitale trombolyse in deze 4 regio's zou de tijd tot behandeling belangrijk verkorten, met een verdubbeling van het aantal patiënten dat binnen 2 uur behandeld zou kunnen worden.

Hoofdstuk 5. Tijd van begin van symptomen tot behandeling en resultaten in prehospitale trombolyse voor het acute myocardinfarct

Het prehospitale trombolyseprogramma heeft een aanzienlijke database gecreëerd van patiënten die binnen 1 en 2 uur na begin van de klachten zijn behandeld. We hebben deze database geanalyseerd voor kenmerken van patiënten met een goede prognose in de vroege behandelingsgroep. Vanaf 1994 tot 2000 zijn in totaal 475 patiënten behandeld voor acute ST elevatie myocardinfarct met prehospitale trombolyse met anistreplase (407 patiënten) of reteplase (68 patiënten); dit nadat de diagnose bevestigd was met een transtelefonisch doorgezonden ECG (*cardiofonie*). Er was geen leeftijdsgrens. Het bestand werd in twee groepen verdeeld: een groep behandeld binnen 2 uur na begin van de symptomen en een groep later dan 2 uur. Als parameters werden de 30-dagen mortaliteit en klinische symptomen van hartfalen gebruikt. Zowel een univariate als een stapsgewijze regressie analyse werden gebruikt om de 30-dagen sterfte uit te zetten tegen leeftijd, tijd tot behandeling, vroeger doorgemaakt infarct, hypertensie, diabetes, hyperlipidaemia, voorwandinfarct, Killip-klasse, systolische bloeddruk en hartfrequentie bij binnenkomst. De totale 30-dagen mortaliteit bleek 9,0% te zijn, waarbij 16,4% van de patiënten hartfalen ontwikkelden. Zowel het hartfalen (12,7% versus 23,2%, $p<0,02$) als de 30-dagen mortaliteit (5,5% versus 15,2%, $p<0,02$) waren significant lager in de vroege behandelingsgroep, vergeleken met de laat behandelden. Leeftijd, tijd tot behandeling, hypertensie en vroeger doorgemaakt infarct waren onafhankelijke voorspellers van 30-dagen mortaliteit. Voor de voorspelling van hartfalen was dit leeftijd, tijd tot behandeling, hypertensie en hyperlipidaemia. Concluderend, prehospitale trombolyse resulteert in een behandeling binnen 2 uur bij tweederde van de patiënten. Onafhankelijke voorspellers voor 30-dagen sterfte waren leeftijd, tijd tot behandeling, een doorgemaakt infarct en hypertensie. Leeftijd, hypertensie, tijd tot behandeling en hyperlipidaemia waren dit voor de ontwikkeling van hartfalen.

Hoofdstuk 6. Het effect van prehospitale trombolyse op het verijdelen van een myocardinfarct

Ervan uitgaand dat het verijdelen van een ST elevatie myocard infarct geassocieerd is met prehospitale trombolyse, hebben we prehospitaal behandelde patiënten vergeleken met in-hospitaal behandelde patiënten. In totaal werden 227 patiënten prehospitaal behandeld in Nijmegen (bolus anistreplase) en retrospectief vergeleken met 269 patiënten die in-hospitale trombolyse ondergingen (1,5 miljoen eenheden streptokinase intraveneus of 100 mg rt-PA, gecombineerd met heparine) in Arnhem. De diagnose verijdeld infarct werd gesteld indien 1) de combinatie van klachten en dynamische ECG-veranderingen overeenkwamen met de verdenking van acuut ST elevatie myocardinfarct, 2) indien de stijging van myocardenzymen in het bloed niet meer was dan twee keer de normaalwaarde en 3) indien de cumulatieve ST veranderingen tot meer dan 50% verbeterden binnen 2 uur na begin van de therapie. Patiënten met onterechte trombolytische behandeling werden uitgesloten, hetgeen in 3 van de prehospitaal behandelde patiënten en 5 van de in-hospitaal behandelde patiënten het geval bleek. In totaal 30 van de 224 prehospitaal behandelde patiënten (13,4%) en 12 van de 266 in-hospitaal behandelde patiënten (4,5%) voldeden aan de criteria van verijdeld infarct ($p<0,05$). Geen van deze patiënten overleed tijdens de ziekenhuisperiode of binnen de 12 maanden follow-up.

Hoofdstuk 7. Uitgebreidere analyse van patienten met verijdeld infarct na reperfusie therapie

Gebruikmakend van een uitgebreider bestand van prehospitaal behandelde patiënten hebben we onderzocht binnen welke tijdslimiet verijdeling van het acute myocardinfarct verwacht kan worden, waarbij tevens gezocht werd naar verschillen in parameters vergeleken met het bevestigde infarct. Van patiënten die verdacht werden van een acuut ST elevatie myocard infarct werden ECG's vanaf de ambulancedienst doorgezonden naar de CCU van één van de 2 Nijmeegse ziekenhuizen. Na bevestiging van de diagnose acuut infarct werden 475 patiënt geïncludeerd en behandeld met trombolyse. De gegevens van deze patiënten werden vergeleken met 269 patiënten die in-hospitaal behandeld waren met streptokinase of rt-PA in een nabijgelegen stad zonder prehospitaal trombolyseprogramma. Een stapsgewijze regressie-analyse werd gebruikt om onafhankelijke voorspellende parameters op het spoor te komen van verijdeling

van infarct. Na correctie voor onterechte behandeling bleken 80 patiënten (17,1%) van de 468 prehospitaal behandelde patiënten en 12 (4,5%) van de 264 in-hospitaal behandelde patiënten te voldoen aan de criteria van een verijdeld infarct. Er was geen verschil in leeftijd, geslacht, risicofactoren en locatie van het infarct bij het verijdelde infarct vergeleken met het bevestigde infarct. Meer dan 30% van de patiënten met een verijdeld infarct had 2- of 3-vatslijden bij coronairangiografie. Behalve de tijd tot behandeling, die significant korter bleek te zijn in de patiëntengroep met een verijdeld infarct, waren eveneens minder ST segment veranderingen en een hogere incidentie op pre-infarct angina pectoris onafhankelijke voorspellers te zijn voor het optreden van een verijdeld infarct. De prognose van een verijdeld infarct is significant beter dan van een bevestigd infarct: de mortaliteit na 12 maanden is 2,2% vergeleken met 11,6%. Concluderend, prehospitale trombolyse is vaker geassocieerd met het optreden van een verijdeld infarct vergeleken met ziekenhuisbehandeling. Een kortere tijd tot behandeling, minder ST segmentverandering en meer pre-infarct angina pectoris zijn onafhankelijke voorspellers hiervoor.

Hoofdstuk 8. Primaire angioplastiek of prehospitale trombolyse en verijdeling van het acute myocardinfarct

Het combineren van prehospitale triage met primaire angioplastiek heeft het tijdsinterval tussen begin van de klachten en mechanisch openen van het afgesloten coronairvat aanzienlijk verkort. We hebben reperfusietijden van primaire angioplastiek en prehospitale triage vergeleken met die van prehospitale trombolyse. De incidentie van het optreden van een verijdeld infarct werd vastgesteld in patiëntengroepen die met één van deze methoden behandeld werden. In totaal werden 545 patiënten prehospitaal behandeld in de steden Rotterdam en Nijmegen en vergeleken met 236 patiënten die met primaire angioplastiek waren behandeld in Zwolle. Alle patiënten waren voorbehandeld met nitroglycerine en aspirine, en de angioplastiekpatiënten met heparine iv. Voor prehospitale trombolyse werd streptokinase of anistreplase gebruikt in Nijmegen of Rotterdam. Als tijd tot reperfusie werd gebruikt de tijd vanaf symptomen tot aan mechanisch openen van het aangedane coronairvat; bij trombolyse werd gebruikt de tijd vanaf begin van de symptomen tot aan behandeling met trombolyse plus 60 minuten. Een verijdeld infarct kwam in 16% van de patiënten voor behandeld met prehospitale trombolyse en in 11% van de patiënten met

primaire angioplastiek. In primaire angioplastiek, bij indeling van de reperfusietijd in vroeger en later dan 2 uur, zagen we significant meer verijdelde infarcten in de vroeg gereperfundeerde groep. De 30-dagen sterfte was niet significant verschillend in vroeg en laat gereperfundeerde groepen, in zowel prehospitale trombolyse als primaire angioplastiek met prehospitale triage. Geconcludeerd, zowel prehospitale trombolyse als primaire angioplastiek is geassocieerd met het optreden van een verijdeld infarct, met vergelijkbare reperfusietijden. In het geval van primaire angioplastiek is de incidentie van het optreden van verijdeld infarct het hoogst in de vroeg behandelde groep.

Hoofdstuk 9. Prehospitale trombolyse met reteplase; de Nijmegen/Rotterdam studie

Teneinde de tijd tot behandeling en de klinische parameters van dubbelbolus reteplase te vergelijken met de reeds gangbare behandeling met streptokinase infuus of bolus anistreplase werd een observationele studie uitgevoerd in twee steden met prehospitale trombolyse (Rotterdam en Nijmegen). Reteplase of streptokinase, dan wel anistreplase werd toegewezen aan patiënten al naar gelang de volgorde van presentatie. Alle patiënten waren voorbehandeld met nitraten en aspirine. In totaal werden 250 patiënten behandeld tussen 1 april 1999 en 1 augustus 2000. Reteplase werd in 120 patiënten gebruikt en de gangbare therapie van streptokinase in Rotterdam of anistreplase in Nijmegen in 130 patiënten. Het gebruik van dubbel bolus reteplase resulteerde in een significant kortere behandelingstijd met een mediaan van 81 minuten vergeleken met een mediaan van 104 minuten met gangbare behandeling ($p<0,05$). Er waren geen verschillen in sterfte, verijdeld infarct, bloedig CVA of de noodzaak tot *rescue*-angioplastiek in beide groepen. Binnen 2 uur was 64% van de patiënten behandeld. Concluderend, dubbel bolus reteplase is geassocieerd met een veel kortere behandelingstijd bij prehospitale trombolyse dan bolus anistreplase of streptokinase.

Hoofdstuk 10. Prehospitale versus ziekenhuistrombolyse met computerdiagnostiek versus diagnostiek a vue van het acute myocardinfarct: verijdeld infarct en onterecht gegeven behandeling

Het doel van deze studie betrof het analyseren van de incidentie van onterecht gegeven fibrinolyse bij een prehospitaal uitgevoerde strategie in Nederland

wanneer verschillende methoden van ECG-diagnostiek worden gebruikt. Onterechte fibrinolyse bij patiënten verdacht voor een acuut myocardinfarct kan desastreus uitvallen, maar moet worden gedifferentieerd van terecht gegeven behandeling die een verijdeld infarct tot gevolg heeft. In Rotterdam werden 118 patiënten prehospitaal behandeld voor acuut ST elevatie myocardinfarct, waarbij gebruik gemaakt werd van een geautomatiseerd computer ECG. In Nijmegen werden 132 patiënten prehospitaal behandeld, gebruikmakend van transtelefonische transmissie naar de CCU en daar beoordeeld door de cardioloog aldaar. De gegevens van deze patiënten werden vergeleken met die van 269 patiënten die in Arnhem in het ziekenhuis werden behandeld, met de overal gangbare methode van beoordeling van het ECG door de cardioloog op de CCU. Alle patiënten werden behandeld met trombolyse volgens dezelfde ECG-criteria. Een verijdeld infarct werd vastgesteld indien er geen stijging optrad van meer dan tweemaal de normale bovengrens van myocardenzymen in het bloed en wanneer minstens 50% van de ECG-afwijkingen verdween binnen 2 uur na toediening. Indien dit niet het geval was werd de diagnose onterecht gegeven fibrinolyse gesteld. Dit trad op in 8 prehospitaal behandelde patienten: 4 in Rotterdam (3,3%) en 4 in Nijmegen (3,0%) en in 5 van de ziekenhuisbehandelde patiënten in Arnhem (1,9%). Een verijdeld infarct werd in 14,4% en 17,4% in Rotterdam respectievelijk Nijmegen tegen 4,5% in Arnhem ($p<0,001$). Concluderend, hoewel het optreden van onterecht gegeven fibrinolyse ongewenst is, gebeurt dit in dezelfde mate in de prehospitale als in de ziekenhuissituatie. Het gebruik van verschillende manieren van ECG-diagnostiek lijkt hierin geen verschil te maken.

Hoofdstuk 11. Kosteneffectiviteit van prehospitale trombolyse

Met behulp van deze studie werd de kosteneffectiviteit van prehospitale trombolyse geanalyseerd, en vergeleken met ziekenhuistrombolyse. Hoewel prehospitale trombolyse gepaard gaat met een tijdwinst van een uur is deze methode van behandeling nog niet algemeen geaccepteerd. Teneinde budgetveranderingen te sturen die voor prehospitale trombolyse nodig zijn, werd een kosten-effectiviteitanalyse uitgevoerd van deze behandelingsstrategie. We hebben twee benaderingen gebruikt. Met een methode werd de mediane tijdwinst van prehospitale trombolyse ten opzichte van ziekenhuistrombolyse toegepast op de met deze tijdswinst geassocieerde risicoreductie, zoals bekend

uit de infarctliteratuur. De kosten van prehospitale trombolyse werden opgeteld bij de 30 dagen sterfte, en de kosteneffectiviteit werd bepaald als de extrakosten van prehospitale strategie gedeeld door het aantal gewonnen levensjaren. Met de tweede methode gebruikten we een wiskundig model om ziektegeschiedenissen van patiënten te simuleren, elk met een bepaald risicoprofiel, met steeds per patiënt twee strategieën: één met prehospitale behandeling en één met ziekenhuisbehandeling. De tijdsintervallen die nodig waren voor deze wiskundige benadering waren gebaseerd op de gegevens van 736 patiënten met een acuut myocardinfarct, 468 prehospitaal behandeld in Nijmegen en 268 in-hospitaal behandeld in Arnhem. Voor het opstellen van de risicoprofielen werd gebruik gemaakt van de TIMI-risikoscore van ST elevatie myocardinfarct. Gebruikmakend van het eerste model, met een risicoreductie van 30% voor in-hospitale behandeling en 35% voor prehospitale behandeling, vonden we een kosten-effectiviteit van prehospitale trombolyse van EUR 2800 per gewonnen levensjaar. Gebruikmakend van het tweede model, met simulatie van ziektegeschiedenissen en bijpassende risicoprofielen, kwamen we uit op een gemiddelde sterfte na 30 dagen van 93,73% met prehospitale trombolyse en van 93,32% met ziekenhuistrombolyse. Dit resulteerde in een kosten-effectiviteit van prehospitale trombolyse van EUR 1837 per gewonnen levensjaar, er van uitgaand dat de gemiddelde levensverwachting van een patiënt 10 jaar is na ontslag uit het ziekenhuis. Concluderend, prehospitale trombolyse is kosteneffectief: EUR 1800 tot 2800 per gewonnen levensjaar, hetgeen zeer goed afsteekt vergeleken met andere therapieën in de behandeling van het acute myocardinfarct.

Conclusies

Tijd tot behandeling in het ST elevatie myocardinfarct is 152 minuten in Nijmegen en varieert van 145 tot 160 minuten in andere regio's. Prehospitale trombolyse in Nijmegen resulteert in een tijd tot behandeling van 89 minuten met een mediane tijdswinst van 63 minuten. Met prehospitale trombolyse kan 28% van de patiënten binnen 1 uur behandeld worden en 65% binnen 2 uur, vergeleken met slechts 25% van de ziekenhuispatiënten binnen 2 uur. In andere regio's zouden 32 tot 51 minuten tijdwinst behaald kunnen worden met een prehospitale strategie, en 55% van de patiënten binnen 2 uur behandeld kunnen worden in plaats van 25%.

Zowel sterfte als het optreden van hartfalen was significant lager in de vroeg behandelde groep (behandeld binnen 2 uur) vergeleken met de groep die later dan 2 uur is behandeld. Leeftijd, tijd tot behandeling, hypertensie en vroeger doorgemaakt infarct waren onafhankelijke variabelen voor de ziekenhuismortaliteit. Leeftijd, tijd tot behandeling, hypertensie en hyperlipidaemia waren onafhankelijke risicofactoren voor het optreden van hartfalen. Het optreden van een verijdeld infarct is geassocieerd met prehospitale trombolyse en treedt in 17% van de gevallen op, vergeleken met 4,5% van de ziekenhuispatiënten, en is verder geassocieerd met een significant betere 1-jaarsoverleving dan het gevestigde infarct (2,2% respectievelijk 11,6%).
Het optreden van een verijdeld infarct komt niet alleen bij prehospitale trombolyse voor, maar ook bij primaire angioplastiek met prehospitale triage. Bij deze laatste behandelingsstrategie is de incidentie van het optreden van een verijdeld infarct significant hoger in de patiëntengroep die binnen 2 uur gereperfundeerd wordt.
Het gebruik van de nieuwe generatie bolus thrombolytica, zoals reteplase, is geassocieerd met een significant kortere behandelingstijd dan met de gangbare infusietherapie met streptokinase, of bolus anistreplase.
Het voorkomen van onterechte fibrinolyse in prehospitale strategie met verschillende methoden van ECG-diagnostiek is niet anders dan bij ziekenhuisdiagnostiek.
Prehospitale trombolyse is zeer kosteneffectief: EUR 1800 en EUR 2800 per gewonnen levensjaar, berekend met behulp van verschillende methoden, en dus goed vergelijkbaar met andere infarctbehandelingen.

Toekomstverwachtingen
Prehospitale trombolyse
Ik hoop met deze dissertatie aangetoond te hebben dat een prehospitale strategie voor trombolysebehandeling essentieel is om de behandelingstijd te verkorten voor het acute ST elevatie myocardinfarct. Desalniettemin ontmoet de implementatie van deze strategie diverse obstakels:
In tegenstelling tot ziekenhuisbehandeling vraagt prehospitale trombolyse om een aanzienlijke investering in tijd, organisatievermogen en geld, bij alle betrokkenen, zoals huisartsen en ambulancediensten.
Veel gezondheidsfunctionarissen, met name ziekenhuismedewerkers, realiseren

zich niet zo dat er aanzienlijke vertragingen bestaan in de behandeling van infarctpatiënten. Wel worden korte transporttijden naar het ziekenhuis benadrukt, maar de substantiële ziekenhuisvertraging gaat veelal ongemerkt.
Er is de angst voor onterechte fibrinolyse bij prehospitale strategie.
Er is onvoldoende consensus over dan wel trombolyse, dan wel primaire angioplastiek, waardoor in bepaalde regio's verdeeldheid optreedt en het implementeren van de ene dan wel de andere strategie wordt vertraagd.

Prehospitale triage

In deze dissertatie wordt het belang van een korte behandelingstijd onderstreept, met eigen onderzoeksgegevens gecombineerd met die uit de literatuur. Prehospitale diagnostiek maakt de weg vrij voor prehospitale trombolyse of snelle primaire angioplastiek. Men dient prehospitale triage regionaal te organiseren, in samenwerking met de plaatselijke ambulancedienst, de plaatselijke ziekenhuizen, de angioplastiekcentra van die regio en de plaatselijke huisartsenvereniging. De Nederlandse Vereniging voor Cardiologie is deze mening eveneens toegedaan en heeft prehospitale triage en trombolyse in de recent bijgewerkt richtlijnen voor het acuut ST elevatie myocardinfarct opgenomen. In onze 15 jaar ervaring met prehospitale trombolyse bleek de samenwerking met de plaatselijke huisartsen van essentieel belang te zijn, met name in Nijmegen waar de huisartsen een belangrijke rol spelen in de eerste opvang van patienten met pijn op de borst. Bovendien bleek de ambulancedienst, meer nog dan andere gezondheidswerkers, zich bewust te zijn van de vertragingen die patienten met pijn op de borst omgeven, en daardoor zeer bereidwillig hun verantwoordelijkheid in de behandeling van infarctpatiënten uit te breiden. Met andere woorden, de implementatie van een prehospitale strategie kan alleen succesvol zijn in samenwerking met de plaatselijke huisartsen en ambulancediensten.

Prehospitale trombolyse en primaire angioplastiek

Veel studies waarin gerandomiseerd wordt tussen ziekenhuistrombolyse en primaire angioplastiek tonen voordelen voor de laatste behandelingsmogelijkheid. Het laatste woord hierover is echter nog niet gezegd, met name indien de resultaten van recent gepubliceerde studies in aanmerking worden genomen, waarbij prehospitale trombolyse, gecombineerd met *rescue* angioplastiek

wordt vergeleken met primaire angioplastiek. Het lijkt zo te zijn dat de reperfusietijd de resultaten gaat bepalen, en niet zozeer de manier waarop reperfusie wordt bewerkstelligd. Met andere woorden: indien de reperfusie tijd van zowel trombolyse als primaire angioplastiek overeen gaan komen, dan is de verwachting dat de resultaten van trombolyse die van primaire angioplastiek gaan evenaren. Bovendien zijn er nieuwe generatie thrombolytica ontwikkeld, die prehospitale behandeling aanzienlijk vergemakkelijken, met daarmee gepaardgaande vermindering van vertragingen in de behandeling. Daarbij komt dat lagere doseringsschema's van trombolytische behandeling gecombineerd kunnen worden met sterk werkende plaatjesremmers zoals de glycoproteine IIb/IIIA receptorantagonisten, waarbij een net zo effectief herstel van de coronairflow verkregen kan worden, maar met een lagere incidentie in het optreden van re-infarcering. Tenslotte, indien men gefaciliteerde primaire angioplastiek wil gaan uitvoeren, dan is prehospitale triage zeer wenselijk, met toediening van trombolyse of GP IIB/IIIA blokker of een combinatie hiervan en transport naar een regionaal catheterisatielaboratorium met ervaren interventiecardiologen; in het geval van trombolyse betekent dit prehospitale diagnostiek en behandeling.

DANKWOORD

Menigeen die na het *The End* van een bioscoopfilm nog even blijft zitten voor de aftiteling, zal zich verbazen over het enorme aantal medewerkers dat nodig is voor de realisatie van zo'n film. Na regisseur, producenten en acteurs wordt meestal een lange reeks namen genoemd, met soms onbegrijpelijke functies erachter, zoals *gaffer*, *clapper loader* en *key grip*. Men realiseert zich aldus dat ieder op zijn of haar manier medewerking heeft gegeven om de film gestalte te geven. Je mag dan nog zulke goede acteurs hebben, en een eersteklas regisseur, zonder de *gaffer* (verlichtingsman), de *clapper loader* (zorgt dat er film in de camera terechtkomt) en de *key grip* (bouwt stellages en rails waarover de camera gereden kan worden en helpt de cameraman hiermee) komt er uiteindelijk niets op het witte doek.

Zo is het in feite ook met het realiseren van een proefschrift. De promovendus is vergelijkbaar met een regisseur, die ook een rol in zijn eigen film meespeelt, en daarnaast zorgt voor *scenario*, *script-editing* en *continuity* op de *set*. Promotor en copromotor zijn de *producer* en *co-producer.* Alle medeauteurs zijn te vergelijken met de acteurs, en de *casting* van de auteurs is afhankelijk van het onderwerp van de film of van het hoofdstuk van het proefschrift. De statistische hulp is misschien nog het best vertaalbaar in de *synchronisation* van het camera- en geluidswerk: zorgen dat de werkelijkheid betrouwbaar op het witte doek of op het papier terechtkomt. En zo kun je nog wel uren doorgaan met fantaseren, maar nu ter zake.

Als je van *producers* van dit proefschrift spreekt dan zijn dit wel Ton Hooghoudt en Don Hertzberger. Beste Ton en Don, jullie hadden de visie om in 1986 met prehospitale trombolyse in Nijmegen te beginnen. Dit was in een tijd met alleen de GISSI studie als bewijsmateriaal, en zonder de geavanceerde apparatuur die er nu is om ECG's over te brengen van thuis naar de CCU. Nog altijd piept en rammelt het ouderwetse faxapparaat, dat toen voor prehospitale diagnosestelling werd aangeschaft, bij mij op zolder. Ook was er maar kort ervaring met streptokinase, en dan alleen in-hospitaal, dus het is niet verwon-

derlijk dat jullie veel weerstand hebben moeten overwinnen om prehospitale behandeling te starten. Financiering van prehospitaal toegediende medicamenten was totaal onduidelijk en de zorgverzekeraars hadden er helemaal geen zin in. Maar jullie hebben doorgezet en dankzij dit pionierswerk is de ervaring opgebouwd die als basis heeft gediend voor dit proefschrift; ik heb erg veel respect voor dit pionierswerk en ben erg dankbaar dat ik de gelegenheid heb gekregen er een proefschrift mee te bewerken.
Mijn promotor professor Freek Verheugt dient eveneens genoemd te worden in de lijst met *producers*. Beste Freek, voordat je naar Nijmegen kwam had je al in een aantal publicaties het belang uiteengezet van de *time to treatment* bij de acute infarctbehandeling. Het is enorm belangrijk dat de regio Nijmegen in zijn geheel kon profiteren van prehospitale therapie, en dat het Academisch Centrum St Radboud met veel enthousiasme aan deze strategie heeft meegewerkt. Ik ben je erg dankbaar voor het vertrouwen dat je in mij als promovendus hebt gesteld. Ik heb heel veel gehad aan je adviezen over de hoofdstukken en je hulp bij de publicaties; voor de vele commentaren en toevoegingen aan de tekst ben ik je veel dank verschuldigd.
En dan de *casting* van acteurs: zonder acteurs geen film en zonder maten geen proefschrift. Naast Ton Hooghoudt en Don Hertzberger heeft ieder van onze maatschap op zijn manier een bijdrage geleverd waar ik erg dankbaar voor ben. Leon Bouwels, Bart-Jan Meursing, Ton Oude Ophuis en natuurlijk ook Jo Tummers, hartelijk dank voor de vele stimulerende woorden en om *stand-in* te zijn wanneer ik weer eens een week montage achter de laptop had gepland. Ieder van jullie is “vereeuwigd” in een stelling. Naast het *producerschap* van Ton Hooghoudt dienen de vele gezellige dagen met hem niet onvermeld te blijven, al dan niet genoodzaakt door presentaties over prehospitale trombolyse, waarbij niet alleen de *script editing*, de *special effects supervision* en het *continuity report* aan de orde kwamen, maar ook tijd werd besteed aan de algemene ontwikkeling. Vooral van de dagen in Berlijn heb ik veel opgestoken, met het bezoek aan het filmpark Babelsberg en de verschillende filmmusea die deze stad rijk is.
Bijna vergeet ik de *stills*: Fred Marcus, Piet en (alweer) Ton Hooghoudt, dank voor de plaatjes! Hartelijk dank voor de medewerking van de andere auteurs: de cardiologen Peter Stolwijk uit Arnhem, Wilma Smits uit Boxmeer, Henk Groeneveld uit Deventer en John van Hal uit Zevenaar. Jullie bijdragen aan de

opbouw van de *time to treatment* hoofdstukken en aan de hoofdstukken over verijdelde infarcten zijn zeer op prijs gesteld. De Rotterdamse cardiologen en hun medewerksters bedank ik hierbij voor hun hulp bij het verzamelen van de gegevens van de Rotterdamse patiënten. Jaap Hartman en Kees de Ruiter van de Rotterdams ambulancedienst moeten even extra worden vermeld. Dr. Eric Boersma, met jouw baanbrekend werk over het belang van de *time to treatment* zou je zeker een *Golden Globe* hebben gewonnen en het Gouden Uur, zoals gepubliceerd in de Lancet, is de basis geweest voor vele hoofdstukken in dit proefschrift; ik ben jou en professor Maarten Simoons erg erkentelijk voor jullie hulp. Datzelfde geldt voor dr. Menko-Jan de Boer uit Zwolle en professor Felix Zijlstra uit Groningen. Dankzij de uitgebreide Zwolse database van infarctpatiënten, behandeld na prehospitale triage met primaire angioplastiek, weten we dat het verijdeld infarct ook in deze patiëntenpopulatie voorkomt. Peter Elsman heeft een sleutelrol hierin gespeeld, waarvoor dank; Peter, leuk dat je in Nijmegen terecht bent gekomen en dat je maar veel rescue- en primaire angioplastieken mag doen. Marc Brouwer uit Nijmegen heeft ook nog een rolletje gespeeld: hartelijk dank voor je steun bij het verdedigen van het concept van het verijdelde infarct. Wij verwachten een filmprijswinnende rolprent van jou. Theo de Boo, statisticus aan de Medische Faculteit, dank voor de regressie-analyses waarmee je beeld en geluid aan elkaar vast hebt geknoopt. De middagen in Utrecht en Nijmegen met kosten-baten-professor Ben van Hout, met de bierviltjesmethode (in hoofdstuk 11 *back of the envelop* methode genoemd) als basis voor de simulatiemethode is mijn inzicht in, en respect voor *health economics* aanzienlijk vergroot. Beste Ben, je hebt het vaak in *slow motion* moeten uitleggen, dank voor je geduld. Wij waren bijzonder verguld dat je ons werk als voorbeeld noemde in je inaugurale rede en ik ben enorm vereerd dat je als *cameo* (hoofdrolspeler die met een bijrol genoegen neemt) in mijn proefschrift hebt willen optreden.
Prehospitale trombolyse staat of valt met de ambulancedienst. Ik speel nu even voor *gaffer* (verlichting) om de Nijmeegse ambulancedienst en die van Grave, onder leiding van respectievelijk Frans Spee, dr. Pierre van Grunsven en Piet Hoving, in de schijnwerpers te zetten. Jullie al vijftien jaar durend enthousiasme voor prehospitale diagnostiek en behandeling heeft uiteindelijk geleid dat in den lande de prehospitale triage en trombolyse routine gaat worden. Ook de huisartsen van de regio Nijmegen, met name Jaap Schreuder te Malden en Paul

Giesen te Nijmegen dienen in het zonnetje gezet te worden. Dat Nijmegen alom in de “prehospitale” literatuur wordt genoemd is voor een groot deel aan jullie te danken.
En nu een *close-up* van Astrid Schut. Astrid, als de functie *key grip* op iemand van toepassing is, dan is dat wel op jou. “*Key*”, omdat je een sleutelfiguur bent geweest in alles wat maar met de organisatie van prehospitale trombolyse in Nijmegen te maken heeft. “*Grip”*, omdat je zowel de successen als de *cliffhangers* in je greep had. Je hebt het ontwerp gemaakt voor de database, mij het gebruik van *Excel* geleerd, met huisartsen en ambulancepersoneel overlegd, met de apotheker, met het Radboud, de tijdsintervallen verzameld, de artikelen doorgenomen, de statistiek nagekeken, posters opgehangen, mij aangehoord als het goed ging, mij ook aangehoord als het niet goed ging en op dat allemaal adequaat gereageerd.
Tenslotte verlaten we studio CWZ en gaan we met de camera (een Debrie Parvo, compleet, te bezichtigen bij Ton Hooghoudt) filmen *on location*. In Den Haag groet ik Hans en Jo Cornet, met een huis vol boeken en een leven vol eruditie. Beste oom Hans en tante Jopie, met alle mooie herinneringen uit mijn jeugd is een prachtige documentaire te vullen. Je zult het nooit zo vermoed hebben maar jullie zijn voor mij altijd een voorbeeld geweest, vooral op die momenten in mijn leven toen ik een voorbeeld zo nodig had. En nu naar de Johannaweg in Nijmegen. Mijn vriend Lee Sallows, vergezeld door twee poezebeesten, wandelt daar in de tuin tussen de *bluebells*. Lieve Lee, dit proef-schrift is één van de projecten die we met zijn tweeën hebben afgerond. Of het nu Toovervierkanten zijn, of “geen dag zonder Bach”, de verbouw van de zolder of de aanbouw van de serre, met de rugzak door de Pindos, of naar *the last homely house east of the sea*, het zijn allemaal weerspiegelingen van een gelukkige tijd. De liefdevolle, sturende en steunende rol die jij in mijn leven speelt komt niet voor in de *credits* van welke film dan ook. Ik ben er dankbaar voor, en trots, als op een Oscar…

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